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Medical News Letter

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MEDICAL NEWS LETTER

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Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, susceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

Change of Address

Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, old and new addresses, and zip code.

FRONT COVER: NAVAL MEDICAL FIELD RESEARCH LABORATORY. This facility is under the command and support of the Bureau of Medicine and Surgery. It was commissioned at Camp Lejeune, North Carolina in August 1943 to conduct research, development and testing in the life sciences, with special reference to the problems in Marine Corps field medicine and amphibious medicine. Over the years its contributions have included development of the minefield boot and the first body armor for modern combat; a new corpsman jacket which is a better container for medical materials; modernized kits for dental operating field sets, a lightweight folding plastic litter; and a portable resuscitator and gas sterilizer. Recently an effective prophylaxis for warm-water immersion foot, a painful condition which disabled many men in Vietnam, was developed. To improve the physical readiness, training and condition of Marines, programs on heat acclimatization have been formulated, and heat stress from various types of body armor is being studied. A new physical readiness test for women Marines was also devised. The Laboratory has studied the etiology of respiratory disease in Marine Corps personnel, and in 1967 confirmed by field trials the safety and efficacy of attenuated live type 4 adenovirus vaccine. The acute respiratory disease rate and the related hospitalization rate dropped dramatically. Studies are continuing on 'T-Strain' Mycoplasma, and agents against meningococcal carriers are being evaluated. Scientists at this valuable research activity have also attacked vigorously the field problem of how to control mosquitoes, lice, chiggers and ticks, and the diseases they transmit. The Laboratory develops and tests clothing and equipment for personnel use and protection, in addition to field medical and dental equipment. Since 1965 it has participated in the development and testing of several large mobile units for the provision of medical and dental care in support of field operations.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

OCCULT GASTROINTESTINAL HEMORRHAGE IN BURNED PATIENTS

D. K. Ousterhout, MD, and Irving Feller, MD, Ann Arbor, Mich.,
Arch Surg 96(3):420–422, March 1968.

One of the most dread complications of the management of the burned patient is gastrointestinal hemorrhage. An accurate evaluation of the incidence of this complication, also known as Curling's ulcer, is difficult. Hummel at the Brooke Army Hospital reported in 1957 a 2 percent incidence of Curling's ulcer in 1,000 consecutive burns (primarily adult males). Choudhury reported in 1963 an 0.09 percent (2) incidence of Curling's ulcer in 2,165 burned children. In 1938 Harkins reported an incidence of 3.8 percent (26) in 680 necropsied burn cases. At the University of Michigan Medical Center, 340 burned patients were admitted from July 1, 1959, to Dec 31, 1965, and of these 2.6 percent (9) developed a Curling's ulcer (unpublished data).

On several occasions it has been noted that the number of blood transfusions necessary to keep the hematocrit at a level of 40 percent is greater than that which would appear to be necessary as a result of red blood cell damage from the burn itself, septicemia, loss of red blood cells through the wound surface, and as a result of blood loss during debriding and autografting. In 1957 Topley and Jackson reported on the loss of red blood cells in burn patients and pointed out that there was an unexplained disappearance of red blood cells in all degrees of burns. However, they did not discuss the loss of RBC via the gastrointestinal system other than to mention two cases of melena in 140 patients they studied. The question was raised as to whether there was occult bleeding through the gastrointestinal system, i.e., whether the Curling's ulcer represents an entity or the extreme example within a spectrum. It was felt that an analysis of stool for blood would offer the best evidence of any condition less than the acute hemorrhage from a Curling's ulcer. The stool guaiac test was selected as the method to determine the presence of occult hemorrhage. Hoerr et al pointed out that positive results on stool guaiac tests in general hospital patients denoted significant organic disease in a high proportion of cases (29) cases of proved intestinal disease in 39 patients having positive stool guaiac tests.

Submitted for publication Aug 21, 1967.
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Materials and Methods

During the one-year period of the study, stool guaiacs were determined on 50 burned patients. Six other patients were admitted during the same period but were excluded because three died shortly after admission before testing could begin and three others had no full-thickness burns.

The study includes 25 male patients and 25 female patients from 6 months to 83 years of age. The burns ranged from 1 percent to 78 percent of the body surface.

An attempt was made to obtain a daily stool specimen from all of the patients in the study, but this was not always possible. While the average duration of hospitalization of the 50 patients was 42 days, an average of only 20 stools per patient was obtained. Most of the specimens were obtained prior to the completion of autografting. Each stool sample obtained was placed in an individual container which was then placed in a refrigerator. Approximately once a week all of the week's samples were analyzed for occult blood. The method for analysis was that described by Page and Culver, except that sodium perborate was used as the oxidizing agent rather than hydrogen peroxide (as described by Bethell and Meyers). Fresh guaiac solution was prepared at least once a month as suggested by Hoerr et al. Stools were considered positive for occult blood if they turned blue or blue-green and were graded as follows: color change in 0 to 1 second, 4+; 2 to 10 seconds, 3+; 11 to 30 seconds, 2+; and 31 to 60 seconds, 1+. Longer than one minute was considered negative for occult blood.

In evaluating the results, 1+ and 2+ gradings were considered nonsignificant. Due to a difference of opinion as to the significance of the 3+ stool guaiac, they were also disregarded for the purposes of this study. Only the 4+ values were used.

A second aspect of the study consisted of reviewing the necropsy protocols and microscopic slides for gastrointestinal hemorrhage and ulceration of 43 burned patients. Fifty-seven burned patients died in the 6½-year period from July 1, 1959 to Dec 31, 1965. Of these 57 patients, 43 (75 percent) underwent necropsy. Fifty other necropsies of nonburned patients were also studied for comparison.

Results

A total of 1,018 stool samples from 50 burned patients were evaluated for occult blood over the period of one year. Of these 1,018 stools, 14.7 percent (150) were graded as 4+. Of the 50 patients, 58 percent (29) had a 4+ result on the stool guaiac test at some time during their hospital course and only 7 percent (2) of these 29 died. The stools became 4+ for occult blood between the second and 22nd day after the injury, the average being eight days. Fourteen female and fifteen male patients had 4+ results on stools tested for occult blood. No differences were noted between age groups. Eight of the patients had burns involving 40 percent or more of their total body, and of these eight, 50 percent (4) had 4+ results on stool guaiac tests. Eighteen patients had burns involving 20 percent to 39 percent of their total body, and 61 percent (11) of these had 4+ stool guaiacs. Twenty-four patients had burns involving less than 19 percent of their total body surface, and 58 percent (14) had four plus stool guaiacs. During the entire study only 0.2 percent (2) stools were melanotic, these being from one patient who was diagnosed as having a Curling's ulcer. Only six stools were simultaneously 4+ stool guaiac and hard in consistency. Of the 50 patients only four (8 percent) died. None of these four was thought to have died from a Curling's ulcer (although one was diagnosed as having a Curling's ulcer), but rather from other complications secondary to their burns.

The necropsy protocols and microscopic slides of 43 burned patients were reviewed for either gross or microscopic evidence of gastrointestinal hemorrhage or ulceration. The presence of petechiae either grossly or microscopically was not considered sufficient for hemorrhage. Twenty-six (60 percent) showed evidence of ulceration, or hemorrhage, or both, while the other 17 necropsies did not show any evidence of either hemorrhage or ulceration. These changes were distributed as shown in the Table.

Comment

Curling's ulcer is a serious complication. Hummel reported that in 20 patients diagnosed as having a Curling's ulcer, 85 percent (17) died. The average survival was 23 days postburn but the average survival posthemorrhage was only four days.

Fifty burned patients and 43 necropsied burned patients were studied to determine whether the Curling's ulcer represented an entity or the extreme example within a spectrum. The results of this study support the thesis that the Curling's ulcer is the end point of a more commonly occurring condition of concealed ulceration and hemorrhage. This conclusion was based on the following: (1) 58 percent (29) of the 50 burned patients were shown to have 4+ stool guaiacs during the course of therapy, and (2) 60 percent (26) of the 43 burned patient necropsies showed evidence of gastrointestinal hemorrhage or ulceration or both. It is interesting to note that the 4+ stool guaiacs were noted on an average of eight days after the burn. In a review of 22 Curling's ulcers, Weigel reported in 1953 that "the usual time of hemorrhage was between the eighth and tenth day."

The amount of blood that is lost by the ulcers and hemorrhage as represented by the four plus stool guaiacs is not known. It would seem to represent a continuous and substantial loss of red blood cells. It would further seem to represent at least a part of the unexplained loss of red blood cells as mentioned by Topley and Jackson.

All patients admitted to the University of Michigan Medical Center Burn Unit since July 1, 1959, have been placed on an intense program of antacids as soon as they are able to take oral fluids. Of the nine Curling's ulcer patients diagnosed at the University of Michigan between July 1, 1959, and Dec

Distribution of Hemorrhage and/or Ulceration in 26 of 43 Burned Patients' Necropsies

Esophagus alone	5
Esophagus and stomach	2
Esophagus, stomach, and duodenum	1
Esophagus and duodenum	1
Stomach alone	3
Stomach and duodenum	2
Duodenum alone	0
Small and large intestine	1
Large intestine alone	2
Other combinations	9
Total	26

31, 1965, none have died of their ulcers. All were managed by a medical program and hemorrhage subsided without operation. However, five of these patients died later from other complications secondary to their burn. Whether this treatment program prevents Curling's ulcers or whether this prevents progression or even the formation of the lesions described in this study is not known. Antacid therapy appears to be indicated until a better method of prevention is presented.

Summary

Curling's ulcer (as presently defined by active gastrointestinal hemorrhage) appears to represent the end point of a more commonly occurring condition of concealed gastrointestinal ulceration with microscopic hemorrhage. This observation is based on the following: The stools of 50 consecutive burn patients were evaluated for occult blood. Of these 50 patients, 58 percent (29) had 4+ results on stool guaiac tests at some time during their hospitalization. Forty-three necropsies of burned patients demonstrated that in 60 percent (26), there was gross or microscopic evidence of gastrointestinal hemorrhage, or ulceration, or both. Continuous antacid therapy is indicated in all burned patients.

(The references may be seen in the original article.)

REVIEW OF AMYLOIDOSIS

Medical Laboratory Quarterly 4(1):1–12, January 1966.

The voluminous, controversial, and often contradictory literature on amyloidosis is testimony to its enigmatic and morassic position in the minds of many physicians. It is the purpose of this brief report to review some of the historical and contemporary thinking of this puzzling disease entity.

The first published description of amyloidosis was by Karl Rokitansky who, in 1842, described its relation to "constitutional diseases of vegetation" including "scrofulosis, rachitismus, inveterate syphilis and quicksilver cachexia." It was not until 1854, however, that Rudolph Virchow coined the term "amyloid," using it to describe the starch-like, waxy material he had observed in the viscera of patients afflicted with long-standing and suppurative diseases. In 1886, Wild published his studies and demonstrated the existence of "primary" and "secondary" forms of amyloidosis. A milestone in our knowledge of amyloidosis was erected by Benhold in 1922, when he described the Congo Red staining method. Apitz' reported in 1940, of the finding of a constant protein moiety in both "primary" and "secondary" amyloidosis, gave new impetus to the study of amyloidosis and on the basis of these findings, he introduced the term "tissue proteinosis." A major advance in our understanding of the etiology of amyloidosis was made by Telium in 1956 when he demonstrated that the "secondary" and experimental amyloid infiltrates which develop after prolonged and excessive antigenic stimulation are formed in situ by cells of the reticulo-endothelial system. He felt that these cells had proliferated and differentiated along "plasmacytic" lines in a manner essentially similar to the normal cellular response to antigenic stimulation. Of major importance was the publication that same year of Vasquez and Dixon's immunohistochemical studies which brought to light the highly specific staining of "secondary experimental amyloid" deposits by fluorescein-labeled anti-normal gamma globulin. More recently, in 1961, Osserman, on the basis of experimental data indicating the close relationship of amyloid and gamma globulin, suggested that the term "gammaloidosis" would be both more correct and more meaningful than the more familiar but less accurate amyloidosis.

Studies supporting the theory that gamma globulin is an integral part of amyloid have been based on the phenomenon of preferrential binding to amyloid deposits of fluorescein-labeled antiserum to gamma globulin or fluorescein-labeled complement.

Amyloidosis may be defined as a disease of unknown etiology characterized by deposits in various tissues of a glycoprotein material immunologically related to normal gamma globulin. The material has an homogenous, eosinophilic appearance when viewed with visible light and often shows characteristic staining reactions consisting of metachromasia with crystal violet and positive staining with congo red.

Our present lack of knowledge precludes a definitive classification of amyloidosis and, therefore, the following clinicopathologic classification is suggested as a practical approach.

Classification:

1. *Generalized Primary Amyloidosis.* The generalized amyloidosis found in the absence of any recognized predisposing disease.

2. *Generalized Secondary Amyloidosis.* Generalized amyloidosis associated with a recognized primary disease.

3. *Amyloidosis occurring with multiple myeloma.*

4. *Localized primary amyloidosis* (tumor-forming amyloidosis). In some classifications this form is included with Generalized Primary Amyloidosis.

As might be expected, a multitude of synonyms have been applied to the above and the same term has been used to designate more than one form or type of amyloidosis. For instance, para-amyloidosis has been used to designate both generalized primary amyloidosis and that type of amyloidosis associated with multiple myeloma. Other symptoms that have been applied to the generalized primary form are idiopathic, systematized, diffuse, atypical, mesenchymatous, essential, vascular mesodermal, malignant, Wild's disease, and Wild-Lubarsch disease.

Similarly, synonyms applied frequently to the generalized secondary form are typical, genuine, visceral, and general parenchymatous.

Generalized Primary Amyloidosis: As would be expected in a disease state involving many organ systems, the clinical manifestations of generalized primary amyloidosis are legion. The onset and progression are insidious. The disease usually appears between the ages of 40 and 80 years, being more frequent in males than in females. The presenting symptoms are usually those of intractable, congestive heart failure with dyspnea, peripheral edema and effusions within serous cavities. Myocardial infarct due to amyloidosis is rare. However, amyloid deposits may be found incidentally within the myocardium of elderly persons. This "senile amyloidosis" is thought to have little effect on cardiac function.

Macroglossia, while not an invariable finding, is frequent and may be striking. This, plus laryngeal involvement, may produce severe dysarthria and dysphagia.

Amyloid deposits are frequently found within the skin and may simulate scleroderma or myxedema. Purpura (due to a selective involvement of the smooth muscle of medium and small sized vessels) is another striking dermatologic finding occurring in approximately one-sixth of cases.

Gastrointestinal hemorrhage is a dangerous complication of generalized primary amyloidosis. These hemorrhages may be due to rupture of esophageal varices produced by hepatic amyloidosis or to ulceration of amyloid deposits within the intestinal mucosa. Chronic diarrhea is another severe complication and may or may not be associated with hemorrhage.

Uremia and the nephrotic syndrome follow diffuse involvement of the kidneys and are a frequent cause of death.

Other less frequent clinical findings are peripheral neuropathy, painful swollen joints, goitre (with or without hypothyroidism), lymphadenopathy, rupture of the spleen or pathological bone fractures.

Microscopically, in these tissues the earliest lesions are found in the interstitial tissue closely applied to reticulin fibers or on the surface of smooth muscle fibers or fat cells. The occurrence of intracellular amyloid is relatively rare. To explain its occasional occurrence there it has been suggested that dying cells become permeable to amyloid. The following chart presents the frequency of distribution of amyloid deposits in 145 cases of primary amyloidosis reported by Symmers.

Treatment for primary systemic amyloidosis is at present limited to symptomatic therapy. Cortisone is contraindicated since it has been found to produce a precipitously fatal course of the disease.

The prognosis in this form of amyloidosis is uniformly poor, death usually occurring within three years from the onset of symptoms.

Generalized Secondary Amyloidosis

Secondary amyloidosis is classically related to long-standing suppurative processes. Chief among these are protracted tuberculous involvement of lungs or bone, chronic osteomyelitis, lung abscess or bronchiectasis. In leprosy, secondary generalized amyloidosis is a major cause of death. And in

Organ	*% with Amyloid*	*Organ*	*% with Amyloid*
Heart	90	Kidneys	35
Gastrointestinal Tract	70	Lungs	30
Tongue	40	Adrenals	25
Spleen	40	Lymph nodes	20
Liver	35	Skeletal muscle	20

familial Mediterranean fever, renal amyloid deposits are a frequent and severe complication. Other conditions with which secondary amyloidosis is frequently associated are hypernephroma, Hodgkin's disease, rheumatoid arthritis, regional enteritis, chronic ulcerative colitis, chronic pyelonephritis, paraplegia with suppurating decubitus ulcers, urinary tract infection, bacterial endocarditis, and severe burns. The distribution of amyloid deposits in secondary amyloidosis has a somewhat different pattern than that found in primary systemic amyloidosis.

Organ	*% with Amyloid*
Spleen	100
Kidneys	93
Adrenals	93
Liver	87
Lymph nodes	68
Pancreas	63

The distribution reported by Dahlin in 30 cases is as follows:

Organ	*% with Amyloid*
Prostate	62
Thyroid	59
Gastrointestinal Tract	55
Heart	43
Lungs	10
Skeletal muscle	0

The symptomatology associated with secondary systemic amyloidosis may frequently be masked by the underlying disease process. However, when prominent, it is related to those organs most severely affected as described in the primary form of the disease. Treatment in this form of amyloidosis should be directed to the predisposing clinical condition. In occasional cases the clinical findings of hepatosplenomegaly and the nephrotic syndrome have regressed completely following treatment of the underlying disease. These cases have not, however, been confirmed histologically. In the usual situation, by the time amyloidosis is clinically apparent, it is no longer reversible.

Amyloidosis with Multiple Myeloma: Approximately 15 percent of cases of multiple myeloma have associated amyloid deposits. The clinical manifestations of these deposits are usually insignificant in relation to the symptoms of the multiple myeloma. The distribution of the lesions and their symptomatology are similar in most cases to those of primary systemic amyloidosis. Occasional cases present the clinical and pathological appearance of secondary amyloidosis.

Localized Primary Amyloidosis: Localized primary amyloid deposits occur in a wide variety of locations. The most common sites are the upper and lower respiratory tract, esophagus urinary bladder and urethra, seminal vesicles, skin and orificial mucous membranes, and in the islets of Langerhans of 50 percent of diabetics over the age of 50 years. The clinical symptomatology of these deposits depends on their size and location. Those deposits in the larynx, for instance, may cause hoarseness. Care must be taken not to diagnose solitary areas of cicatrix formation or focal hyalinization of collagen as areas of localized primary amyloidosis. The special diagnostic procedures to be discussed below must be done before a diagnosis can be made.

Etiology and Pathogensis: Although a wide variety of etiological factors and pathogenetic mechanisms have been proposed to explain the nature and occurrence of amyloid deposits, all have proven deficient in one aspect or another.

The various contributing factors that these efforts have brought to light include the response to prolonged antigenic stimulation, the amount of protein in the diet, the ability of Vitamin C deficient diet to produce amyloid deposits, and the relationship to diseases of protein metabolism. These have helped pave the way to the recent discoveries of Vasquez and Dixon, Williams, Calkins, and many others. These workers have shown experimentally that stimulation of the RE system with foreign protein results in the formation of glycoprotein substances which react immunochemically as does amyloid, and that these substances at the same time are closely related to normal gamma globulin. Immunoelectrophoretic comparisons made by Cathcart, et al, differentiated amyloid fibrils separated by differential centrifugation from other serum protein constituents. The material separated by them from a case of secondary amyloidosis had the electron microscopic appearance of amyloid, and reacted with Congo Red to give green birefringence in polarized light.

Antibody prepared to this soluble fraction gave distinct precipitin lines on Ouchterlony plates, and migrated as a fast alpha globulin in agar and polyacrylamide gel. This fraction was found as a minor serum constituent in apparently healthy individuals as well as in pathologic states.

While these studies do not provide definite proof that amyloidosis is an autoimmune disease, they do provide promising fields of investigation for the future.

Tests Used in the Diagnosis of Amyloidosis: A wide variety of the tests are available to aid in the

clinical diagnosis of the various forms of amyloidosis. Although these tests vary considerably in their specificity, when taken together and correlated with the patient's clinical status, they are of considerable value in the establishment of a diagnosis.

Blood studies often show a progressive hypochromic anemia. However, a hemolytic type of anemia has also been described. Alkaline phosphatase and BSP retention may be elevated when hepatic amyloid deposits are extensive. Serum globulins are usually increased but may be low in the face of a complicating nephrotic syndrome. Serum albumin is usually low. Hypercholesterolemia is frequently found, but its level is variable.

There is no characteristic urinary sediment. Albuminuria may or may not be severe and may be accompanied by increased urinary globulins.

Congo Red: Under normal conditions almost all of the intravenously administered dye is excreted by the liver into the bile. At the end of one hour after administration of the dye approximately 70 percent to 90 percent of the dye remains in the blood stream of normal patients. The dye will, however, be cleared rapidly from the serum of patients who have secondary amyloidosis. Levels of 20 percent to 40 percent retention are considered to be suggestive of secondary amyloidosis. Retention of more than 40 percent of the injected dye is interpreted as negative for amyloidosis.

While the above guidelines to interpretation of the Congo Red test are useful, they must be exercised with a view to the clinical state of the patient. Congo Red is transported in the blood absorbed to the albumin faction of the plasma proteins. In the nephrotic syndrome the dye disappears from the blood rapidly but is excreted with the albumin in the urine. In the nephrotic syndrome associated with amyloidosis, much less of the dye will be excreted in the urine. Furthermore, low levels of retained dye may be found in patients with hypoalbuminemia without albuminuria. Finally, careful note should be taken that there is no consistent relationship between the rapidity of the removal of the dye from the blood and the extent of the amyloid deposits in the tissues.

A radioiodinated Congo Red test is used in some experimental models, but it is at present no more specific than the routine Congo Red test. The staining of amyloid deposits associated with multiple myeloma is notoriously erratic. It is for this reason that the term paramyloid has been applied to them.

Evans Blue Test

Evans Blue, a dye previously used in blood volume studies has been recently reported to be useful as an aid in the diagnosis of secondary amyloidosis. Larsen and Farnum have reported that this dye is non-toxic and is rapidly fixed to amyloid deposits. Amyloidosis is inferred if the concentration of Evans Blue is less than 90 percent of the 10-minute concentration after 30 minutes and less than 83 percent after 60 minutes.

They also feel that a positive result may be recorded if the initial distribution volume of Evans Blue exceeds that of labeled albumin by more than 16 percent.

Biopsy: Numerous sites have been recommended for diagnostic biopsies. These sites include the rectum, small bowel, gingiva, liver, spleen, kidney, bone marrow, and conjunctiva.

Rectal biopsy will reveal amyloid deposits in the vascular walls of the mucosa and submucosa in approximately 75 percent of cases. Peroral small bowel biopsies also reveal vascular involvement but, in addition, may reveal some amyloid in the basement membranes of the crypts. Gingival biopsies are usually positive only in secondary amyloidosis and even then in only 20 percent of the cases. Needle biopsy of the kidney is considered more rewarding than needle biopsy of the liver or spleen.

In the kidney, amyloid is deposited chiefly in the glomeruli and blood vessel walls. The glomerular deposits are found beneath the capillary endothelium. The splenic involvement may be focal or diffuse. In the focal form (sago spleen) the deposits first appear in arteriolar walls and then extend into adjacent lymph follicles. In the diffuse form the splenic reticulum is involved, but the lymph follicles are spared. Hepatic amyloid deposits first appear in a mid-zonal lobular distribution in the space between the sinus endothelium and the hepatic cells. As the deposits increase in size pressure atrophy of the surrounding parenchymal cells occurs.

The diagnosis of amyloidosis in the autopsy room may sometimes be made by exposing a fresh-cut surface to Lugol's solution. It is stated that the amyloid will appear a dark-brown color. If the Lugol's solution is followed by 1 percent sulphuric acid, the brown color may turn a light blue. This test is of limited value since the reaction is variable. In general, organs diffusely infiltrated with amyloid deposits are somewhat enlarged, firm, and have a pale coloration.

Ultrastructure of Amyloid: Paul and Cohen, investigating the ultrastructure of amyloid with ferritin conjugated antibody, demonstrated that amyloid deposits of diverse origin contain fibrils of constant cross-sectional diameter. Their studies included amyloid from cases of primary, secondary, experimental, and genetic (associated with familial Mediterranean fever) amyloidosis. They were unable to identify, immunologically, gamma globulin as an intrinsic component of the fibrils since ferritin conjugated anti-human gamma globulin did not adhere to the fibrils. A suggested explanation for this finding is that the gamma globulin, if present, was denatured during tissue processing and unable to react.

Histochemistry of Amyloid: Although the exact nature of amyloid remains a mystery, it is presumed to be composed of a glycoprotein immunologically related to normal gamma globulin. The components thus far identified within amyloid are trypsin, glycine, alanine, valine, leucine, cysteine, methionine, hexosamine, and hexuronic acid.

There are no stains or histochemical procedures which can be used singularly and in a specific way to identify amyloid. With hematoxylin and eosin, the material appears as a pale pink homogenous substance. Fortunately, amyloid exhibits some staining characteristics which, if used with other clinical and laboratory data, will serve to separate it from other abnormal protein deposits. The following table enumerates these reactions:

1. Metachromatic staining.
2. Strong affinity for Congo Red and Evans Blue.
3. Negative birefringence in an unstained state.
4. Positive birefringence and dichroism if stained with Congo Red.
5. Strong secondary fluorescence in ultraviolet light after staining with Thioflavin–T.
6. A high degree of resistance to extraction with proteolytic enzymes such as pepsin.

Metachromasia is defined as the staining of a tissue component in such a way that the absorption spectrum of the resulting tissue-dye complex differs sufficiently from that of the original dye and from its ordinary tissue complexes to give a marked contrast in color. Metachromatic staining reactions are given by the triphenylmethane dyes, methyl violet and crystal violet. The basis for their reaction with amyloid is probably the presence of free electronegative surface charges on the mucopolysaccharides present in the amyloid. Those substances not showing a metachromatic reaction take a blue stain. Those substances which do show the reaction may evidence a range of color from purple (a weak reaction) to red or pink (a strong reaction).

Some investigators have reported that amyloid is exclusively stained with crystal violet when ionic strength and pH are carefully controlled. A prominent drawback to the metachromatic staining procedure is its lack of permanence.

While the Congo Red stain is permanent, it stains many other normal substances such as elastin, mucin, cartilage, and the granules of eosinophiles. In addition, Congo Red stains abnormal materials such as hyalinized collagen and fibrinoid deposits.

The basis for the ability of Congo Red stained amyloid to evidence birefringence is apparently the formation of a crystal-like lattice with the ability to rotate plane-polarized light. It should be noted that fixation of the tissues in mercury containing solutions such as Zenker's and Helly's solutions will inhibit the birefringent reaction.

It is important to remember that prolonged formalin fixation of tissues will inhibit the Congo Red test.

The use of the Thioflavin–T reaction produces consistent results in many laboratories; however, the reaction tends to fade rapidly. Amyloid stained with Thioflavin–T gives a bright yellow to yellow-green fluorescence when viewed with a darkfield condenser and ultraviolet light. Some difficulty with residual stain may be encountered on the elastic lamellae of small arteries and with intestinal mucus. This may be avoided to a significant degree by thorough washing with water betwen each step of the staining procedure. With this technique sections may be rapidly reviewed and small amyloid deposits readily identified. The lack of permanence of the stain is a minor drawback to the procedure.

Of the above staining reactions, the dichroic reaction of amyloid when stained with Congo Red is probably the most specific.

Although amyloid is not significantly affected by pepsin digestion, the reaction is diagnostically useful in that the pepsin will digest out fibrin, "fibrinoid" tubular casts, the "hyaline droplets" of kidney tubular epithelium, and the hyaline substance of scar tissue.

Summary

Improved understanding of amyloidosis is expected as more refined techniques of study are ap-

plied. As with many other diseases that have initially been shrouded by a confusion of synonyms and myopic reports, this condition is beginning to succumb to a multidisciplined scientific approach. A relationship to normal body constituents has already been indicated. The final elucidation of the underlying biochemical aberraton will doubtless shed an equal amount of light on the normal life processes.

(The references may be seen in the original article.)

PARENTERAL CEPHALORIDINE TREATMENT OF PATIENTS WITH EARLY SYPHILIS

J. M. Glicksman, MD; D. H. Short, MD; and J. M. Knox, MD,
Houston, Arch Intern Med 121(4):342–344, April 1968.

Cephaloridine was administered to 23 patients with early infectious syphilis, and observed for a minimum of 12 months after treatment. Clinical, darkfield, and serological results have been excellent with no observed allergic reactions or untoward effects. Included were five patients with known penicillin allergy. Two patients demonstrated Herxheimer's reaction. The results thus far are excellent but the drug still requires continued investigation over a longer period of time.

Cephaloridine, produced by a strain of *Cephalosporium acremonium,* is a broad-spectrum antimicrobial agent effective against many gram-positive and gram-negative organisms. Its direct bactericidal effect against *Treponema pallidum* is perhaps the most fascinating discovery from the cephalosporin C series of antibiotics. Fortunately, it can be used in patients with syphilis who are allergic to penicillin because no cross-sensitivity between cephaloridine and penicillin has been noted.

Gallo et al have demonstrated in vivo and in vitro bactericidal effects of cephaloridine in experimental syphilis. Seftel et al reported a satisfactory clinical and serological response in 21 patients with early syphilis treated with doses of cephaloridine ranging from 0.5 gm twice daily for five days to 1 gm daily for ten days. Ochoa and Cravioto reported one patient with secondary syphilis treated satisfactorily with 0.5 gm cephaloridine twice daily for three days.

The problem of penicillin allergy is increasing. Paralleling this problem is the increasing incidence of pregnant patients with syphilis who are sensitive to penicillin. A completely safe and effective alternate antibiotic is sorely needed but not yet available. The untoward effects of effective alternate antibiotics presently used for pregnant patients are well documented. These include changes in fetal teeth and long bones as well as damage to the maternal liver and kidneys.

South et al reported a case of secondary syphilis in a young pregnant woman successfully treated two months before her delivery with 500 mg of erythromycin estolate three times daily for ten days (total 15 gm). Although syphilis in the mother was arrested, the infant developed congenital syphilis and died during the third day of life. Penicillin readily crosses the placenta to achieve a serum concentration in the infant of approximately one-half that of the mother. In contrast, erythromycin estolate is reported to attain fetal serum concentration of only one-fifth to one-sixteenth that of maternal serum concentration.

This report presents data from a study presently under way at the Houston Social Hygiene Clinic evaluating cephaloridine as an alternate antibiotic in 23 patients.

Method

The study includes 23 patients seen in the Houston Social Hygiene Clinic with darkfield positive primary or secondary syphilis or with darkfield negative secondary syphilis who showed typical lesions along with a high titer serological test. Immediately after diagnosis an attempt was made to evaluate the patient's willingness to cooperate and to return for treatment as well as for follow-up examinations.

Each patient received 0.5 gm of cephaloridine intramuscularly daily for ten days skipping Saturday and Sunday. During and after completion of therapy all patients were questioned to determine if they had developed any side effects from the drug. The

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follow-up program included daily darkfield examinations until negative, monthly serological examinations, and a lumbar puncture 12 months after treatment.

Only patients with primary (ten patients) or secondary syphilis (thirteen patients) who have been observed at least 12 months are reported in the tabulation. An additional 15 patients have been similarly treated, yet they are not included in this report because they were lost to follow-up or have not been followed for the minimum period of 12 months. To our knowledge, there have been no therapeutic failures in this group either.

The criteria for therapeutic success was established as follows: Therapy would be classified as "failure" if (1) the lesions did not heal; (2) lesions reappeared; (3) serologic titer did not diminish, or (4) serology relapsed. The occurrence of one or more of these eventualities would have constituted a failure. Any distinction between reinfection and relapse was to be based upon clinical judgment and all such cases were to be classified as "retreated."

Results

In the 23 patients treated with cephaloridine there were no treatment failures and none were "retreated." Daily darkfields were usually negative within 24 hours from the time of treatment and always negative in 48 hours. Spirochetes, if present after 24 hours, were always few in number and poorly motile. The serologic response was satisfactory in all 23 patients (Table).

Two patients had typical Herxheimer reactions following their first injecton of cephaloridine. Five patients were known to be hypersensitive to penicillin; however, none of these patients noted any unusual or untoward side effect.

Of the three patients who experienced undesirable symptoms while being treated, none had a previous history of drug hypersensitivity. One complained of headache, one of pruritus, one of dizziness and pruritus. The patient with the headache obtained relief with 5 grains of aspirin although the study drug was continued. Both patients with pruritus obtained relief after therapy with bath oil was begun even though treatment with cephaloridine was continued.

We believe that the symptoms these three patients experienced were coincidental and not a direct result of taking the drug. The pruritus was probably related to xerosis ("winter itch") caused by a marked drop in the outdoor temperature and humidity.

Comment

The results indicate that cephaloridine is an effective and safe alternate antibiotic for patients with syphilis who are allergic to penicillin. Clinical, darkfield, and serological data thus far are satisfactory in our series of patients treated with cephaloridine. To be certain that the long-term results are equally satisfactory, these patients are still being followed.

No cross-reactivity between cephaloridine and penicillin was noted by us or by previous authors. Such a reaction certainly appears to be feasible, however, because penicillin and cephalothin cross-react. Also, cephalothin and cephaloridine cross-react (Griffith, R. S., written communication, October 1966).

Cephalothin is closely related to cephaloridine in the cephalosporin C series of antibiotics. Tso Sheng et al have demonstrated in a study of 19 normal pregnant women in active labor that cephalothin is transmitted through the placenta and yields high levels in the cord blood as well as in the amniotic fluid. Human fetal serum concentration of cephaloridine is not known at this time. We expect that placental transmission of cephaloridine would approximate that of cephalothin since these two drugs are so closely related. The serum level of cephaloridine is twice the level of cephalothin after the same intramuscular dosage. Also the level of

Synopsis of Serological Responses in Eary Syphilitic Patients Treated With Cephaloridine

		Months, VDRL*				
Patient	Diagnosis	0	3	6	9	12 or More
1	1	64	2	WR	0	NR
2	1	R	NR	NR	NR	NR
3	1	32	WR	NR	0	NR
4	1	16	WR	NR	NR	NR
5	1	WR	NR	0	0	NR
6	1	8	R	0	WR	NR
7	1	16	R	NR	NR	NR
8	1	R	NR	NR	NR	NR
9	1	NR	NR	NR	NR	NR
10	1	4	WR	NR	NR	NR
11	2	32	WR	NR	WR	NR
12	2	256	0	0	0	NR
13	2	8	2	R	R	R
14	2	32	4	4	0	WR
15	2	32	0	R	R	R
16	2	16	0	WR	WR	NR
17	2	32	WR	NR	WR	NR
18	2	32	4	2	R	R
19	2	16	2	2	2	2
20	2	32	2	R	R	WR
21	2	32	NR	NR	0	NR
22	2	32	2	WR	WR	NR
23	2	32	4	R	WR	R

* VDRL indicates venereal disease research laboratory test for syphilis; R, R Undiluted (1:1); 32, 1:32, 16, 1:16, etc (refers to number of dils or titer) VDRL; 0, not done; WR, weakly reactive; NR, nonreactive; 1, primary syphilis; and 2, secondary syphilis.

antibacterial activity in the serum after cephaloridine administration is sustained longer. Welles et al have demonstrated the passage of cephaloridine to the fetus and in milk in rabbits.

The next step in this study will be to evaluate cephaloridine in patients with syphilis during pregnancy. It is hoped cephaloridine will prove to be a satisfactory alternate antibiotic for treatment of pregnant patients who are allergic to penicillin.

An additional case of syphilis treated with cephaloridine was brought to our attention by a recent communication from Harris D. Riley, Jr., MD, of the Department of Pediatrics, University of Oklahoma Medical Center, Oklahoma City. A 2-month-old, 4.42-kg (9 lb 12 oz) patient with clinical and serological evidence of congential syphilis was treated on May 17, 1967, with 200 mg of cephaloridine every eight hours intramuscularly for two weeks (total dose 8.4 gm). The initial response to treatment has been satisfactory. Follow-up continues.

The cephaloridine used in this study was supplied as Loridine by Eli Lilly & Company, Indianapolis through R. S. Griffith, MD.

Generic and Trade Names of Drugs

Cephaloridine—*Loridine*.
Cephalothin sodium—*Keflin*.
Erythromycin estolate—*Ilosone*.

(The references may be seen in the original article.)

CLINICAL EXPERIENCE WITH THE USE OF FROZEN BLOOD IN COMBAT CASUALTIES *

LCDR Gerald S. Moss, MC USNR, LCDR C. Robert Valeri, MC USNR, and CDR Charles E. Brodine, MC USN, New Eng J Med 278(14):747–752, April 4, 1968.

In January, 1966, at the request of the Department of Defense, the United States Navy Bureau of Medicine and Surgery established a frozen-blood facility at the Navy Station Hospital, DaNang, Republic of South Vietnam. This facility was to receive a limited supply of Group O, Rh-negative blood that had been frozen in the United States for use in selected casualties in DaNang. The objective was to define the potential of frozen blood in expanding the capability and flexibility of the existing blood-banking system.

It is the purpose of this paper to report the first clinical experience with frozen blood in a combat zone, with special reference to its role in that setting. Freezing and reconstitution of the cells was accomplished according to the method described by Huggins.

Materials and Methods

Collection of Blood

Units of Group O, Rh-negative, Kell-negative, Duffy-negative red cells were collected in acid citrate dextrose solution (NIH A), with the co-operation of the Massachusetts Red Cross Blood Program, the Massachusetts General Hospital and the United States Naval Hospitals in Chelsea, Massachusetts, and Beaufort, South Carolina.

Glycerolization and Shipment

Processing of the frozen red cells was performed at the Blood Research Laboratory, United States Naval Hospital, Chelsea, Massachusetts, and the Frozen Blood Laboratory at the Massachusetts General Hospital as follows:

Within five days of collection, the red cells were separated from the plasma, placed in a specially designed freezing bag (Blood Freezing Unit)** and glycerolized by the addition of a solution containing 8.6 M glycerol in 8 percent glucose, 1 percent fructose and 0.3 percent disodium ethylenediaminetetraacetic acid (Na_2EDTA). The sugars maintained osmotic equilibrium, and the EDTA prevented the development of Coombs-positive red cells. After 10 minutes of mixing, the bags were folded flat and placed in a —80°C freezer. The blood was sub-

* From the Bureau of Medicine and Surgery, Navy Department, Research Task No. MR005.19–0004 (address reprint requests to LCDR Moss at the Experiment Surgery Division, Naval Medical Research Institute, Bethesda, Md. 20014).

The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

**International Equipment Company, Needham Heights, Massachusetts (Model PR–2).

sequently packed in dry ice in polystyrene foam boxes and air-shipped to DaNang. Frozen blood was stored at the United States Naval Hospital, Oakland, California, and the United States Naval Hospital, Subic Bay, Philippines, for rapid resupply.

The Frozen-Blood Facility

The frozen-blood facility in DaNang was made up of two air-conditioned vans: one for processing and storage, and the other for laboratory work. The former housed a −80°C freezer with a 100-unit capacity,* two PR–2 refrigerated centrifuges,† two small Jewett blood refrigerators,‡ and a Huggins 5-module cytoglomerator.§ The laboratory van contained a Coleman Jr. spectrophotometer,¶ a phase microscope, ‖ a Barnstead still,** an autoclave†† and equipment for routine hematology.

Personnel consisted of one medical officer, one laboratory officer and two technicians, all of whom, in addition to their duties in the blood bank, carried out general hospital duties.

Reconstitution

Just before transfusion the unit was thawed in a 37°C water bath for three to five minutes; 500 ml of 50 percent dextrose was added to the thawed cells, which were then washed and recovered by agglomeration three times on the cytoglomerator with a total of 6000 ml of 8 percent glucose, 1 percent fructose solution over a 20-minute period. After resuspension in 250 ml of isotonic saline solution the unit was centrifuged, the supernatant extracted into a satellite transfer pack, the final unit volume weighed, a 5-ml sample withdrawn from the unit for hematocrit and total hemoglobin concentration, and a 10-ml aliquot of the supernatant collected for hemoglobin concentration determinations. As many as 5 units could be processed simultaneously. Most transfusions were carried out shortly thereafter.

In almost all units, the processed cells underwent a formal crossmatch including saline, albumin and Coombs technics. Since the reconstituted Group O, Rh-negative red cells were suspended in glucose-saline solution containing virtually no isoagglutinin, it was possible to use them for any recipient, irrespective of his blood group.

In Vitro Data

The units were studied for in vitro loss of red blood cells as follows:

$$\% \text{ loss red blood cells} = 100 - \left[\frac{\text{cellular Hgb in final bag} \times 100}{\text{cellular Hgb in original bag}}\right]$$

Cellular hemoglobin is defined as the difference between total and supernatant hemoglobin. The percent red-cell loss calculated in this manner includes cells lost as a result of transfer from one container to another, from sampling and from freeze-thaw hemolysis.

The amount of supernatant hemoglobin present in each of the packed red-cell units was calculated by multiplication of the concentration of supernatant hemoglobin by the volume of the supernatant in the unit.

The Clinical Setting

The casualties, many of whom were severely injured and in shock, were off-loaded from helicopters in the hospital landing area frequently only minutes after injury. In the receiving wards they were placed on stretchers and rapidly examined. Airway exchange was assured, external hemorrhage was controlled, chest catheters were inserted when required, and intravenous therapy was initiated. Resuscitation was initiated with balanced salt solution. Mannitol and sodium bicarbonate were liberally used. After careful crossmatching, blood, either frozen-processed or ACD (acid citrate dextrose, Formula A), was administered via a No. 15 polyethylene catheter over a period of 10 to 15 minutes under pressure with the use of an external cuff on the plastic bag.

The ACD Blood Bank was supplied primarily with Groups A and O blood, plus smaller amounts of Groups B and AB. Rh-negative blood was available in limited quantities. In most cases Group A and AB recipients received ACD A, whereas Group O and B recipients received ACD O.

In Vivo Data

Patients included in this report were intensively monitored throughout their hospital stay in DaNang. Whenever possible, blood and urine specimens were collected before and immediately after a series of transfusions.

Serial microhematocrits were obtained to estimate the effect of the transfusion. However, because of

* Harris Manufacturing Company, Incorporated, Cambridge, Massachusetts 02139 (Model 17L–2–DR).
† International Equipment Company, Needham Heights, Massachusetts (Model PR–2).
‡ Refrigerator Company, Incorporated, Buffalo, New York (Model CT–1).
§ International Equipment Company, Needham Heights, Massachusetts (Model WS–5 [60 cycle]).
¶ Coleman Instruments, Incorporated, Maywood, Illinois (Model 6A).
‖ American Optical Company, Buffalo, New York (Micro-Star Series 10).
** Barnstead Distiller, Forest Hills, Boston, Massachusetts (Model 210).
†† American Sterilizer Company, Erie, Pennsylvania (Type 32–D).

the large volume of nonred-cell-containing fluids used for resuscitation, this measurement was not helpful.

Blood was drawn for determinations of plasma hemoglobin immediately before and after a series of transfusions, and daily thereafter, by means of No. 18 needles, heparinized syringes and saline-rinsed test tubes. At the same time, samples of urine were collected to determine urinary hemoglobin. In selected casualties, serum hemoglobin-binding capacity (serum haptoglobin) was measured. Serum bilirubin was measured approximately six hours after a series of transfusions and daily thereafter. Other studies included measurement of serum creatinine, platelet count and urinalysis daily.

Results

Over the first seven months of 1966, 2,586 transfusions were administered at the Naval Station Hospital. Eighteen percent of these were frozen-processed cells. This report includes data on 36 patients who received a total of 307 units of frozen-processed cells and 347 units of ACD blood. Total storage time for the frozen-processed cells before transfusion ranged from four to eight months. Total reconstitution time ranged between 45 and 60 minutes.

For purposes of data analysis, all units of blood given within a 24-hour period were evaluated collectively in each recipient. During a 24-hour transfusion period, the recipient received frozen-processed cells only, ACD blood only, or a combination of both.

Table 1 shows the volume and distribution of blood administered. It should be noted that most of the frozen-processed units were given to the most severely injured combination group.

In Vitro Studies

The mean in vitro red-cell loss, measured in 72 units, was 26.7 percent (±12.8 percent). This value is nearly identical to the loss recorded at the United States Naval Blood Research Laboratory, Chelsea, Massachusetts, where long-distance shipment was not involved, and is higher than that reported by the processing laboratory at the Massachusetts General Hospital. The mean supernatant hemoglobin, measured in 226 units, was 54 mg (± 47 mg).

TABLE 1. *Volume and Distribution of Blood Transfused*

Character of Blood Transfused	No. of 24-Hr. Transfusion Periods	No. of Units Transfused	Mean No. of Units/ Transfusion Period
Frozen blood only	37	132	3.6
ACD blood only	14	161	11.5
Combination	20	361	18.1
(a) Frozen		(a) 175	(a) 8.8
(b) ACD		(b) 186	(b) 9.3
Totals	71	654	

The final volume of the "average" frozen-processed unit was 210 ml, with a hematocrit of 87 percent. High hematocrits were selected to minimize the amount of supernatant hemoglobin in each unit by reducing the supernatant volume. Despite this hematocrit level, the application of external pressure on the bag produced rapid flow rates.

In Vivo Studies

Table 2 shows the change in recipient plasma hemoglobin measured immediately after transfusion. It should be noted that elevation per unit was small after the transfusion of ACD blood, as opposed to a value of 3.68 mg per 100 ml for recipients receiving frozen-processed cells. The six-hour post-transfusion elevation in recipient serum bilirubin was 0.12 mg per 100 ml per unit of ACD blood given, 0.28 mg per 100 ml per unit of frozen-processed cells given and 0.07 mg per 100 ml per unit for the combined use of ACD blood and frozen-processed cells.

Figure 1 reports the highest serum creatinine observed in each patient plotted against the volume of blood administered during in-country hospitalization in 20 of the most seriously injured who received a combination of frozen-processed red cells and ACD blood. The average amount of blood given was 30 units. Serum creatinine was determined daily for a mean of six days. None of the patients observed in the study had acute renal failure despite the massive nature of many of the injuries. The two highest values, 4.7 and 3.1 mg per 100 ml, were seen in patients with lethal injuries who died within 48 hours of injury. The patient who received the largest volume of blood, 93 units, of which 41 were frozen, survived, his highest creatinine value being 1.9 mg per 100 ml.

Figure 2 reports the relation between the lowest recipient platelet count within 24 hours of transfusion and the number of units transfused. These recipients received either ACD blood alone or a combination of ACD and frozen blood. In both groups there was a decline in recipient platelet count as the volume of transfused blood increased. The calculated line of regression is almost identical in these two groups.

Hemoglobinuria was noted in nine cases as shown in Table 3. In each, onset was within 48 hours of

TABLE 2. *Elevation of Recipient Plasma Hemoglobin* *

Character of Blood Transfused during 24-Hr Treatment Period	Mean Plasma Hemoglobin Elevation/ Unit	Mean Plasma Hemoglobin Elevation/ Treatment Period	No. of Units/ Treatment Period	No. of Units Transfused	No. of Treatment Periods	No. of Patients
	Δmg/100 ml	*Δmg/100 ml*				
ACD only	0.72	14.99	15.1	106	7	7
Frozen only	3.68	10.02	3.4	115	34	25
Combination (ACD & frozen)	1.30	23.02	18.6 { ACD 9.9 / frozen 8.7	334 { ACD 156 / frozen 178	18	15

* Samples obtained before & immediately after transfusion.

TABLE 3. *Observations in Casualties in Whom Hemoglobinuria Developed*

Patient No.	Plasma Hemoglobin *mg/100 ml*	Urinary Hemoglobin *mg/100 ml*	Highest Serum Creatinine *mg/100 ml*	Units of ACD Blood *	Units of Frozen-Processed Cells *	Survival
1	6.7	5.1	2.7	22	16	Yes
2	7.3	14.0	1.6	40	16	Yes
3	8.8	7.7	3.1	0	11	No
4	10.1	58.0	1.1	18	3	Yes
5	16.3	70.9	1.5	5	15	Yes
6	17.8	74.0	1.5	34	0	Yes
7	40.0	32.8	1.6	10	10	Yes
8	50.1	72.0	1.4	9	10	Yes
9	102.0	235.0	1.9	6	16	No

* Total volume of blood received at time hemoglobinuria detected.

admission. At least 11 units of blood had been administered before the appearance of hemoglobin in the urine. The low plasma hemoglobin values in six of the casualties measured at the time hemoglobinuria was detected suggest a loss of plasma hemoglobin-binding capacity. This was documented in four of the patients in whom plasma hemoglobin-binding capacity was measured. Also shown in Table 3 is the highest serum creatinine noted in each of the nine casualties while he was hospitalized in Vietnam.

Discussion

The combat-zone blood bank, situated at the end of a long supply line, often receives blood 10 to 12 days after collection. Demands for blood are sporadic and unpredictable. At the same time, adequate reserves must be available to deal with any crisis. Loss of liquid-preserved blood due to outdating, under these circumstances, is unavoidable. By means of low-temperature storage, it is possible to prolong red-cell shelf life. Extensive in vitro and in vivo studies and clinical evaluation of the frozen-processed agglomerated red cells have been carried out at the Blood Research Laboratory, United States Naval Hospital, Chelsea, Massachusetts, since 1963. Red cells preserved by freezing and stored for more than two years have met the most exacting laboratory and clinical criteria and have been found to be acceptable for transfusion. The results of these studies, in large measure, led to the establishment of the Frozen Blood Facility in DaNang.

In the present study the mechanism of removal of the nonviable cells was evaluated by measurement of plasma hemoglobin and bilirubin levels. If a considerable amount of intravascular hemolysis occurs, a rise in recipient plasma hemoglobin is observed in excess of that attributed to the hemoglobin in the donor plasma. Cassell and Chaplin, in studying 42-day-old ACD blood, reported that any elevation in recipient plasma hemoglobin could be accounted for by the hemoglobin in the donor plasma and that there was essentially no intravascular lysis of nonviable erythrocytes. Almond and Valeri arrived at a similar conclusion in the study of frozen-processed cells. Both papers dealt with small-volume transfusions in stable patients.

In this study, in which multiple units of frozen-processed cells were given to acutely injured casualties, the mean elevation of recipient plasma

hemoglobin was 3.68 mg per 100 ml per unit of transfused frozen-processed cells. If an average adult plasma volume of 3000 ml is assumed, the mean observed amount of extracorpuscular hemoglobin appearing in the intravascular space was 3.68 x 30 = 110.4 mg. On the basis of the measured mean supernatant hemoglobin value for the transfused units, the expected amount of extracorpuscular hemoglobin appearing in the intravascular space should have been 54 mg. The difference, 56.4 mg, represents an unexplained elevation in recipient plasma hemoglobin of only 1.9 mg per 100 ml. These observations suggest that the bulk of the nonviable cells were removed by other than an intravascular mechanism. Regarding extravascular hemolysis, the small elevation in post-transfusion recipient serum bilirubin suggests minimal extravascular hemolytic activity. These changes noted in both recipient plasma hemoglobin and serum bilirubin offer indirect evidence of acceptable in vivo survival of the frozen-processed cells.

The creatinine observations indicate that renal insufficiency was rarely seen in the badly injured recipient. Renal function in traumatic shock depends upon a number of variables, including location and extent of injury, magnitude and duration of shock, adequacy of fluid therapy and quality of the transfused cell. Experience in World War II and the Korean conflict suggested that renal insufficiency was a major problem in the severely wounded, accounting for a significant mortality and morbidity. The fact that renal insufficiency was not as frequent in this study is probably a result of the shortened evacuation time and improved resuscitative technics in general.

The decline in recipient platelet count suggests that the thrombocytopenia observed with massive transfusions may be viewed as both a depletional and a dilutional phenomenon—that is, blood with viable platelets is lost through hemorrhage or peripheral entrapment. The replacement with either multiple units of stored ACD blood containing nonviable platelets, or frozen blood with no platelets, results in a similar decrease in recipient concentration. In a study conducted during the Korean conflict, Scott and Crosby reported generally elevated platelet counts in a group of 11 casualties who received 6 to 16 units of blood. The difference between their observations and ours may be due to a difference in patient selection. In the present study, as shown in Figure 2, many of the casualties received far more than 16 units of blood, thereby implying that, as a rule, they suffered more extensive injuries, lost more blood and received more transfusions.

Hemoglobinuria was observed in nine casualties who required extensive replacement therapy with either frozen-processed cells or ACD blood or both. The appearance of free hemoglobin in the urine is primarily the result of the interplay of two variables: the reabsorptive capacity of renal tubules for free plasma hemoglobin; and the hemoglobin-binding capacity of the plasma. The latter is related to an $alpha_2$ globulin haptoglobin, which has been shown to bind free hemoglobin. Normally, free hemoglobin in the plasma is bound to haptoglobin, and the resultant complex cannot be filtered by the glomerulus. Clearance is by way of the reticuloendothelial system. When plasma hemoglobin values exceed the hemoglobin-binding capacity of the plasma, the free hemoglobin fraction is filtered and excreted by the kidney, if the tubular reabsorptive capacity is exceeded. If the plasma hemoglobin-binding capacity has been depressed, even minor elevations in plasma hemoglobin may result in hemoglobinuria, as was noted in six of the casualties. In this group of nine patients, the relation between hemoglobinuria and impaired renal function was not considered statistically significant with the use of the Fisher exact test (1 tail), where $p = 0.089$. It should be stressed that special emphasis was placed upon the inducement of adequate urinary flow during initial resuscitation with saline infusion, in addition to the prompt administration of mannitol.

The studies carried out in DaNang concerning the in vitro red-cell loss indicate that $-80°C$ storage temperature can be satisfactorily maintained with dry ice during air shipment. Previous studies have shown that inadequate agglomeration during the initial washing phase of the processed unit may be the result of poor preservation technics or faulty storage. A low ionic environment in the wash solution is necessary for satisfactory agglomeration. Unsatisfactory agglomeration under these circumstances appears to be due to a movement of intracellular ions into the wash solution. The dependency of agglomeration on low ionic environment functions as a built-in safety mechanism because units that do not agglomerate rapidly are discarded. Unsatisfactory agglomeration was noted in less than 1 percent of the units processed in DaNang.

The major usefulness of a frozen-blood capability in a combat zone can be simply defined. It provides a stable, readily available source of compatible cells. During the course of the study, a number of observations on this point were made. First of all,

with a reserve of 100 to 200 units of frozen Group O, Rh-negative blood, only a moderate supply of ACD blood need be on hand, thus creating the potential for reduced loss from out-dating. Secondly, during mass casualties, frozen-processed cells can be fed into the ACD system, supporting in part a number of patients of different blood groups, since all recipient blood groups were compatible. Thirdly, the Rh-negative recipient can be singled out for support with frozen-processed Group O, Rh-negative cells because, as a rule, supplies of ACD, Rh-negative blood are limited in the field. Without a frozen-blood capability, it is likely that Rh-negative recipients would receive Rh-positive blood, especially if massive amounts were required. Of course, compromises are necessary in the field, and, in general, this one is well tolerated. However, in the acutely sensitized recipient who has been massively transfused, it is possible that anti-Rh antibodies will develop at the very time when a significant portion of his red-cell population is Rh positive. Moreover, if a patient should subsequently be typed as Rh positive, he might be given additional units of Rh-positive blood. In either situation, serious hemolytic reactions may develop.

Basically, what has been described is an alternative to the walking donor system. Why should an alternative be desirable? In the first place, it is a major undertaking to obtain adequate numbers of donors, particularly at night. Communications have to be dispatched to surrounding installations when sufficient hospital personnel are not available. Armed vehicles are necessary at night to transport the donors back and forth. The risks of such an undertaking are readily apparent.

Secondly, many of the men are unsatisfactory donors in Vietnam. The plague vaccine has been recently shown to contain an A substance capable of inducing significant titers of natural and immune-type agglutinins and immune-type hemolysins in Group O persons. Safe universal-donor blood is therefore difficult to obtain. Not infrequently, the donor may have a significant degree of dehydration. Syncope after collection under these circumstances is not uncommon. In addition, malaria and hepatitis are endemic in the area.

The principal indication for the use of walking-donor blood at the Station Hospital in DaNang is thrombocytopenia occurring during resuscitation of the badly injured casualty. Other labile clotting factors can be supplied with fresh-frozen AB plasma.

These initial observations of the operation of a frozen-blood-bank system in a combat zone have demonstrated both clinical acceptability and technical feasibility. It is realized that an ideal system does not yet exist. The major efforts in the future will be devoted toward reduction in the volume of wash solution required, shortening of the reconstitution time and improvement in the in vitro recovery rate of red cells.

This report would be incomplete if mention were not made of the outstanding performance of the Army 406th General Medical Laboratory, Camp Zama, Japan, in supplying ACD blood. Resupply was regular and in the appropriate amount and distribution. Emergency response was dependable and rapid. We are especially indebted to the commanding officer, LCOL J. Metzger, MC, USA, and to LCOL Frank Keil, MC, USA, as well as to CAPT B. Canaga, MC, USN, senior medical officer, and the medical staff of the Station Hospital, DaNang, and to LTJG J. F. Bates, MC USNR, Roger LaRouche, HM2, Kenneth Fowler, HM2 and Miss Linda McCallum for technical assistance.

(The omitted figures and references may be seen in the original article.)

PULMONARY EMBOLI MASQUERADING AS ASTHMA *

Francisco Olazábal, Jr., MD, Luis A. Román-Irizarry, MD, Jorge D. Oms, MD, Lillian Conde, MD, and Ernesto J. Marchand, MD,
New Eng J Med 278(18):999–1001, May 2, 1968.

Bronchoconstriction is a nearly constant sequela to acute pulmonary embolism, and wheezing was recently reported as occurring in some patients suspected of having this disease. To our knowledge, however, there are no clinical reports establishing angiographically the diagnosis of pulmonary embol-

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ism in patients presenting apparent bronchial asthma. During the last four months we have proved this diagnosis in three patients initially treated for bronchial asthma.

Case Reports

Case 1. A 46-year-old nurse reported to the Employees' Clinic at the San Juan Municipal Hospital on August 25, 1967, with a recurrent episode of "asthma." She was found to have generalized wheezing and was treated with epinephrine, aminophylline, diphenhydramine hydrochloride (Benadryl) and amobarbital sodium (Amytal sodium). The patient did not respond in the usual fashion and was admitted to the hospital later that day. On admission she gave a history of asthma as a child, with remission in early adolescene. The attacks had recurred 2 years previously, when she was hospitalized elsewhere for "bronchitis," and again during the last 3 months, when she was treated repeatedly at the Employees' Clinic. A carefully taken history revealed thrombophlebitis of the right leg before the recurrence of wheezing in 1965 and the onset of precordial nonpleuritic chest pain and dyspnea on the day before the present admission.

Physical examination disclosed generalized expiratory wheezing, moist rales in the left, and decreased breath sounds in the right posterior aspect of the chest. There were 2 tender cords and a positive Homans sign on the right leg. X-ray films of the chest revealed a radiolucent area in the right-lung base, and pulmonary scanning demonstrated decreased uptake in the middle inferior portion of the right lung. Three days after admission, after wheezing had entirely subsided, a pulmonary angiogram demonstrated a negative filling defect at the pars basalis of the right pulmonary artery proximal to its bifurcation and marked delay and diminution of blood flow to the lower half of the right-lung field. There was also segmental oligemia to the lower part of the left lung.

The patient was given heparin and did well, except for an episode of hemoptysis. Ten days after admission, nausea and vomiting, chest pain, and pain in the right leg suddenly developed, and tachycardia, tachypnea, diaphoresis and respiratory rhonchi were found. During the next day, despite adequate anticoagulation 2 similar episodes occurred, and there was a rise in the lactic dehydrogenase (LDH) determinations to a maximum of 720 units. On September 5 the inferior vena cava was ligated. The postoperative course was uneventful, and she was discharged on October 2. Repeat lung scans revealed gradual improvement in uptake at the previous "cold" areas, and by October 9, the lung scan was entirely normal.

Case 2. A 56-year-old woman was seen at the Emergency Division of the San Juan Municipal Hospital on August 28, 1967, with generalized malaise, fever and chills of 5 and nonpleuritic chest pain and dyspnea of 4 days' duration. There was a history of asthma since childhood, but she had been asymptomatic for the last 10 years. On initial examination generalized wheezing was found, and she was treated with intravenous infusions of fluids and aminophylline. Subsequently, she was admitted to the hospital, where examination revealed moderate respiratory distress with a pulse of 110, a temperature of 100°F, slight neck-vein engorgement, inspiratory and expiratory wheezes and sinus tachycardia. The white-cell count was 11,400, with 6 percent band forms, 58 percent neutrophils, 3 percent lymphocytes and 2 percent eosinophils. Initial x-ray films showed an infiltrate in the superior segment of the right lower lobe. An electrocardiogram disclosed a QRS axis of $+80°$, with prominent P waves in Leads 2, 3 and aVF. On the day after admission the serum glutamic oxalacetic transaminase (SGOT) level was 74 units, and the LDH level 950 units. A lung scan demonstrated decreased uptake at the middle lower field of the right lung, and pulmonary angiography revealed a negative filling defect at the origin of the left pulmonary artery and amputation of the branch to the lateral basal segment of the right lower lobe. Heparin was given, and the hospital course was uneventful although repeat lung scan on September 4, 1967, showed an additional area of decreased uptake at the lower portion of the left lung.

Case 3. A 22-year-old woman was seen at a local dispensary on October 12, 1967, with the acute onset of wheezing and was treated with intravenous infusion of fluids and epinephrine. After a good response she was sent home but returned a few hours later with a generalized urticarial reaction. An injection of diphenhydramine hydrochloride was followed by a syncopal episode, and she was referred to the San Juan Municipal Hospital. On arrival examination of the medical record showed a previous hospital admission 2 weeks post partum in May, 1964, with the diagnosis of pulmonary embolism. She had had 3 distinct embolic episodes during the hospital course, with typical findings on history, physical examination, x-ray films, electrocardiogram and laboratory tests. The highest LDH level reported was 1220 units. Anticoagulants were given

for 2 years, but she was then lost to follow-up observation. Additional information revealed that severe, pleuritic, left precordial pain and dyspnea had suddenly developed on the day before admission.

Physical examination showed an obese woman in moderate respiratory distress. There was sinus tachycardia, tachypnea with respirations of 36 to 40, generalized wheezing, an accentuated 2d component of the 2d sound and tender swelling of the right calf. X-ray films of the chest were normal, but pulmonary scanning demonstrated a marked decrease in uptake of the entire left lung. An angiogram indicated a considerable decrease in blood flow to the left lung. Anticoagulants were given, and the hospital course was uneventful.

Discussion

Subclinical bronchoconstriction is frequently present in patients with pulmonary embolism. As early as 1920 Dunn described histologic changes in lungs subject to thromboembolism, suggesting the possibility of bronchospasm. Boyer and Currey, in 1944, demonstrated transient bronchoconstriction in dogs subjected to pulmonary embolism but believed that, because of its transient nature, the bronchoconstriction was of little practical importance. In 1963 Gurewich and his co-workers demonstrated, by pulmonary-function tests, the presence of bronchoconstriction in seven patients suspected of having pulmonary embolic disease, and proposed the diagnostic use of these tests.

Audible wheezing, however, has only rarely been reported in patients with pulmonary embolism. Its frequency in pulmonary embolic disease is unknown, and some recent reviews fail to mention wheezing as a sign in this disease. Gurewich et al. found clinical wheezing in only one of their patients and commented on another patient, not included in their study, in whom recurrent wheezing had been a prominent feature and who, at postmortem examination, was found to have multiple pulmonary emboli. In 1966 Webster and his associates reported three cases of wheezing in patients suspected of having had pulmonary embolism. The diagnosis was based on the clinical picture and abnormal lung scans, but there was no pathological nor angiographic confirmation. It is now known that the pulmonary scan, although of great value as a screening procedure, is nonspecific. Furthermore, acute bronchial asthma may produce an abnormal scan. Indeed, bronchial asthma and pulmonary emphysema must be differentiated from pulmonary embolism as causes of abnormal scans in patients wtih negative x-ray studies. The lack of a past history of bronchial asthma in the cases of Webster et al. was considered to be important in ruling out intrinsic asthma as the cause of wheezing.

During the last year we have performed selective pulmonary angiography in 25 patients suspected of having pulmonary embolic disease. Wheezing was a prominent sign in eight patients, and in several others localized wheezing was found. The three cases reported above were regarded as apparent bronchial asthma; the patients were initially treated with bronchodilators and were subsequently proved angiographically to have had pulmonary embolism.

It has been known for centuries that wheezing may occur in patients with cardiac failure. Until the present, patients first seen by the physician with recurrent episodes of generalized severe wheezing were suspected of having either bronchial or cardiac asthma. These patients with severe dyspnea are usually unable to give an adequate history, and to make the differential diagnosis, a search for various physical signs, the measurement of circulation times and therapeutic trials have been proposed. We have demonstrated above that pulmonary embolic disease can also appear occasionally in this fashion. To emphasize this relation, we have coined the term "embolic asthma." The frequency of embolic asthma in patients suspected of having bronchial or cardiac asthma is unknown, but it is probably high. Congestive heart failure predisposes patients to the development of pulmonary embolism, and it is of interest that some patients regarded in the past as having cardiac asthma have clinical pictures very suggestive of pulmonary embolism. A history of previous bronchial asthma is probably significant in patients without heart disease. In these cases the target organ is probably more susceptible to the bronchoconstrictor substances released during embolization. In the near future, as we examine these patients in more detail, the true frequency of each of these conditions will be estimated.

At present certain features suggest to us the diagnosis of embolic asthma. Recurrent attacks of asthma after years of minimal or no symptoms are suggestive of pulmonary embolic disease. Patients with recurrent asthma after adequate management, with status asthmaticus or with recent onset or aggravation of symptoms should be evaluated carefully; the presence of chest pain, either pleuritic or anginal, must be explained. All patients with cardiac asthma should be suspected of having had pulmonary embolism.

Once the diagnosis is suspected, elevated lactic dehydrogenase levels or an abnormal pulmonary scan persisting after wheezing has subsided is the best screening test for pulmonary angiography, which must be carried out to establish the diagnosis without question in these cases. The response to heparin has been suggested as having differential value. Wheezing in our patients usually subsided after heparin anticoagulation was begun, but at present it is not clear whether this was the result of therapy.

(The figures and references may be seen in the original article.)

MEDICAL ABSTRACTS

MEDICAL MANAGEMENT OF CHRONIC RENAL FAILURE

W. B. Schwartz, MD, and J. P. Kassirer, MD, Amer J Med 44(5):786–802, May 1968.

The recent advent of new and dramatic forms of therapy, such as chronic dialysis and transplantation, has altered the outlook for a small but significant number of patients with chronic renal failure. The prospects for home dialysis and for improved methods of tissue typing give grounds for optimism that definitive treatment of the uremic state will ultimately be available to a much larger number of people than is currently feasible. Despite these expectations the fact remains that for some time to come the mainstay in the treatment of most uremic patients will be careful medical management designed to extend survival and to make life more tolerable. For this reason an understanding of the many abnormalities that occur in uremia remains a matter of prime clinical importance. This paper is designed to review current knowledge that provides the basis for the rational management of the uremic state.

MITHRAMYCIN THERAPY IN DISSEMINATED GERMINAL TESTICULAR CANCER

N. W. Ream, MD, et al., JAMA 204(12): 1030–1036, June 17, 1968.

Mithramycin, an antibiotic, was used in the treatment of 30 patients with disseminated germinal testicular cancer. The antitumor effect of mithramycin was evaluated in 26. Nine patients experienced an objective antitumor response, which has been complete in two. The major responses occurred in patients with embryonal carcinoma with pulmonary metastases. No significant response was observed in patients with advanced retroperitoneal or hepatic metastases from embryonal carcinoma or in the six patients with teratocarcinoma. The toxicity of mithramycin encountered in this investigation does not preclude employing this agent as a primary treatment of metastases from embryonal carcinoma of the testis.

NATURAL HISTORY OF GARDNER'S SYNDROME

CAPT K. E. Thomas, MC USAF, et al., Amer J Surg 115(2):218–226, Feb 1968.

Two families with Gardner's syndrome have been investigated. Studies demonstrate that colonic polyposis may not be inevitable in a member of a family with the syndrome, possessing an external manifestation. Similarly, if one of the external manifestations is absent, polyposis may still be present. Roentgenograms of the long bones and digits are as important as those of the mandible and skull for establishment of the syndrome. The biologic behavior of colonic polyps occurring with Gardner's syndrome and with familial polyposis is identical with respect to age of onset, propensity for regression after ileoproctostomy, and age at death. Although the behavior of the polyps is identical, the gene transmitting the two diseases is probably dissimilar. When clinically feasible, the authors would advocate partial colectomy with low ileorectal anastomosis as the preferential treatment for polyposis in Gardner's syndrome.

THE CLINICAL SPECTRUM OF PRIMARY TUBERCULOSIS IN ADULTS

W. W. Stead, MD FACP, et al., Ann Intern Med 68(4):731–745, Apr 1968.

Thirty-seven adults with tuberculosis are reported, in whom there was evidence (usually tuberculin conversion) that infection was of primary type. The clinical spectrum of primary tuberculosis ranges from a total lack of symptoms in most to massive miliary tuberculosis in a few. Between these ex-

tremes, 9 were observed with minor clinical illness accompanied by parenchymal infiltrate, 11 with pleural effusion, and 16 with chronic tuberculosis. Chronic lesions appeared in some at the site of the primary implantation but were more common in the apex, probably because of hemotogenous seeding there in the course of the primary infection.

Of particular interest were 16 patients in whom primary tuberculosis progressed within a few months or years into chronic pulmonary tuberculosis; reinfection appeared to play no role. Such progression supports the "unitary concept" of tuberculosis recently advocated.

Whenever tuberculin-negative persons (even adults) are exposed to an open case of tuberculosis, infection may take place and be treacherous: primary tuberculosis is difficult to recognize because of mildness or illness, tendency to spontaneous "healing," and lack of prior tuberculin data in most cases. Despite absence of initial illness, primary tuberculosis may progress either sooner or later to chronic tuberculosis. Prevention of serious complication of primary infection can be accomplished by two means: vaccination of persons who must be exposed in work (Peace Corps workers, etc.) with Calmette-Guérin bacillus to prevent infection, or prophylactic chemotherapy with isoniazid (INH) for those in whom infection has already occurred.

INTOLERANCE TO ASPIRIN

M. Samter, MD FACP, and R. F. Beers, Jr., MD
Ann Intern Med 68(5):975–983, May 1968.

Angioedema and rhinitis, nasal polyposis, and bronchial asthma of aspirin-sensitive patients are acquired diseases that develop, as a rule, after middle age in predominantly nonatopic patients. In many instances, nasal and bronchial symptoms precede the development of intolerance to aspirin by months or even by years. Salicylates other than acetylsalicylic acid fail to produce symptoms in aspirin-sensitive patients. Exposure to several chemicals, on the other hand, that are structurally unrelated to aspirin can induce comparable "aspirin-like" symptoms. The structural dissimilarity of these compounds is so pronounced that immunological cross-reactivity appears most unlikely. The substances that have been found to induce aspirin-like symptoms have one characteristic in common—they are strong minor analgesics and include pyrazolones and indomethacin as well as aspirin. Peripheral analgesics might act on peripheral chemoreceptors and initiate a series of reflexes that might produce either angioedema, or rhinitis and bronchial asthma, or all of these.

DENTAL SECTION

RETENTIVE QUALITIES OF NON-VERTICAL, NON-PARALLEL PLACED PINS

LCDR R. J. Koss, DC USN, and
LCDR E. M. Osetek, DC USN.

Although no studies have been made to support the hypothesis, it is generally believed that the retentive qualities of a pin-retained restoration are enhanced if the pins are not parallel to the direction of force. The purpose of this study was to determine whether the angle of pin placement actually does affect the retention of a restoration. Eighty samples simulating cuspless teeth were prepared in ivorine, and a pin-retained amalgam restoration was placed on each sample. Variables were the use of either two or four Unitek or Threadmate Minim pins, and placement of the pins at depths of 2 or 4 mm in the ivorine. Ten samples of each type were prepared, in five of which the pins were placed parallel to the direction of force, and in the other five the pins were placed at a 15-degree angle to the direction of force. The retentive qualities of each type were tested by determining the weight required to separate the restoration from the ivorine. With the Unitek pins, doubling their number doubled their retentive qualities, but varying the depth of placement had no effect. With the Threadmate Minim pins, retentive qualities increased with both the number of pins used and depth of placement. However, in one condition only where Threadmate Minim pins were placed nonparallel to the direction of force at a depth of 4 mm, there was significantly less retention than where placed parallel at the same depth. With all other variables, there was no significant difference between the retentive qualities of pins as a result of their being placed parallel or nonparallel to the direction of force. It was concluded that pins should be placed parallel to the direction

of force when possible, but that the angle of pin placement has little practical effect on the retentive qualities of Unitek and Threadmate Minim pins.

(Abstract by Research Work Unit: MR005.19–6052 by LCDR R. J. Koss, DC, USN, and LCDR E. M. Osetek, DC USN.)

PERSONNEL AND PROFESSIONAL NOTES

RADM FRANK M. KYES RECEIVES THE LEGION OF MERIT

Citation:

For exceptionally meritorious service from 1 August 1963 to 18 July 1968 as Assistant Chief of the Bureau of Medicine and Surgery (Dentistry), and Chief, Dental Division, Bureau of Medicine and Surgery, Navy Department, Washington, D.C. During this period, Rear Admiral Kyes was responsible for the establishment of the Preventive Dentistry Program, which has significantly reduced tooth decay among active duty personnel and their departments. He was instrumental in revising the policy of recruit dental care to insure that personnel reporting to operating units will be in a state of dental fitness which contributes materially to fleet readiness and combat effectiveness. Through the development of Mobile Preventive Dentistry Units and the "Whole Ship Concept" of dental treatment, Rear Admiral Kyes has simplified administrative procedures and has eliminated unnecessary steps, resulting in savings of thousands of man-hours. Many other innovations by Rear Admiral Kyes have contributed materially to improved patient care, and have enabled the U.S. Naval Dental Corps to provide a variety of additional, intangible services to Navy personnel. His sincere concern for the welfare of all men, and deep compassion for the problems of others are qualities that have inspired subordinates and greatly enhanced the morale of those serving in the Naval Dental Corps. Through his inspiring leadership, sound judgment, and dedication to the principles of his profession, Rear Admiral Kyes has upheld the highest traditions of the United States Naval Service.

AMERICAN SPECIALTY BOARDS

The following listed officers of the Naval Dental Corps have recently met the requirements for certification as Diplomates of the respective American Specialty Boards:

American Board of Oral Surgery

CDR Ronald D. Baker DC USN
CDR Norman K. Luther DC USN
LCDR John S. Lindsay DC USN

American Board of Periodontology

CAPT Frank Dobronte DC USN

American Board of Prosthodontics

CAPT Stephen O. Bartlett DC USN
CAPT Ronald C. Smith DC USN
CDR Kenneth E. Brown DC USN
CDR David M. Grove DC USN
CDR Dean L. Johnson DC USN
CDR James E. Miller DC USN
CDR Virgil A. Pinkley DC USN

GRADUATION AT THE NAVAL DENTAL SCHOOL

On June 21, Doctor Harold Hillenbrand, Secretary of the American Dental Association, gave the graduation address on "Dental Health Problems of Today" at a ceremony for 43 Dental Corps officers who had completed long graduate-level courses and residencies at the Naval Dental School.

In reviewing the progress of dental education at the School since 1923, Doctor Hillenbrand said the original mission of the Naval Dental School—continuing education and the training of dental auxiliary personnel—is embodied in the mission of dentistry today.

Presentations of the following awards were made to outstanding graduates: the Surgeon General's Award for Scholastic Achievement, for attaining the highest scholastic average, to LCDR David J. Smith; the Commanding Officer's Award for Excellence in Operative Dentistry, to LCDR Paul S. Hatrel; and the Naval Dental School Award for Achievement in Research Methods, to co-winners CDR Richard S. Davidson and LCDR Richard G. Preece.

PROFESSIONAL JOURNALS NEEDED

The Naval Dental School needs the following listed issues of professional journals:

Journal of Oral Surgery, Anesthesia and Hospital Dental Service

1963 January
1964 May and July

Journal of Oral Surgery

1965 January
1966 September
1967 January and July

Journal of Oral Surgery, Oral Medicine and Oral Pathology

1963 January, February, April, May, June, July, August, September, November
1964 January, February, March, April, May, October, November, December
1965 January, February, March, May, June, September
1966 May
1967 February

If anyone has any or all of these editions he would donate to the School, please contact the Commanding Officer (Code E4), Naval Dental School, National Naval Medical Center, Bethesda, Maryland 20014.

OCCUPATIONAL MEDICINE SECTION

HIGHLIGHTS OF FLUORIDE TOXICOLOGY

Harold C. Hodge, PhD, Rochester, New York, JOM 10(6):273–277, June 1968.

The continued and increasing use of fluorides makes timely a brief resumé of some of the highlights of fluoride toxicology.

Fluoride, biologically, is a ubiquitous bone seeker with a variety of physiologic and toxic effects some of which constitute substantial hazards if neglected, but also with properties which permit a ready control of the hazards and an assurance of safety. Six properties have been so well studied that they may serve as landmarks of fluoride toxicology; these will be discussed in some detail.

Acute Poisoning: The certainly lethal dose for the standard 70 kg adult man is estimated to be 2,500 to 5,000 mg F. Because sodium fluoride is roughly half F, the lethal dose is 5 to 10 g of sodium fluoride or 1 to 2 teaspoonfuls. The course of acute poisoning is rapid. Taken orally, death often occurs in 2 to 4 hours; many patients who live longer than 4 hours recover. The reasons for the rapidity are not hard to find: in high concentrations fluoride is a powerful metabolic inhibitor. Rapid absorption and rapid distribution throughout the body of a lethal or near lethal dose quickly permit dangerously high concentrations of fluoride ion to develop. Patients surviving for 4 or more hours have an improved prognosis because fluoride is rapidly deposited in the skeleton and rapidly excreted in the urine thereby decreasing blood and tissue concentrations below fatal levels.

Toxic doses of fluorides taken orally have a salty or soapy taste; nausea, vomiting, diarrhea, cramping develop promptly; with large enough doses, collapse, coma and death ensue. Death is usually attributed to a blockade of necessary enzyme or transport systems; which such system(s) are responsible for death cannot be said. Calcium-binding by overwhelming doses of fluoride probably accounts for the unclotted state of the blood reported in some autopsy examinations.

Kidney: When experimental animals are maintained for periods of months on diets or on drinking water containing over 100 ppm F, various changes in kidney structure and function can be demonstrated. Tubular cells die and regenerate, interstital fibrosis develops, and in some animals a remarkable dilatation of certain tubules begins in the loop of Henle, later involving the distal convoluted tubule. Such dilated tubules have not been reported in man; in fact the only kidney effects ascribed to prolonged human exposures to fluorides are those in certain hospitalized patients in India or China with diagnoses of skeletal fluorosis who exhibited reduced kidney function (e.g., urea clearance). In certain patients suffering from advanced kidney disease, or in animals with specifically injured kidneys (such as occurs

in uranium poisoning), the ability to excrete fluoride in the urine is not seriously impaired until the kidneys fail. In terminal uremia, fluoride is excreted more slowly than usual, blood fluoride levels increase and, as a result, the concentrations of fluoride in the skeleton increase markedly.

Thyroid: Many studies have been made of the effects of fluoride on the thyroid, perhaps partly because fluoride's being a halogen raised the question whether fluoride, like iodine, might be taken up preferentially and stored by the thyroid. It is not. Perhaps interest in the thyroid has continued because textbooks have quoted an observation made years ago of a struma or goiter in a dog repeatedly given very large doses of fluoride. Large amounts of F do alter the thyroid. More than 50 ppm F in the ration or drinking water administered over periods of days to years have been responsible for structural or functional changes in the thyroid in a number of species of animals. When the diet contained less than 50 ppm of fluoride, few thyroid alterations were found.

Growth: The dairy cow, the most sensitive species, given a ration containing 40 ppm of fluoride for four or five years will lose weight and become unthrifty. Other species studied sustain growth impairment only with higher levels of dietary fluoride. If a single report by Japanese investigators is discounted, no adverse effects on human growth are known.

On the other hand, reliable evidence of the normal growth of children in a fluoridated community has been gathered. Possible growth effects of fluoride consumed at 1 ppm in the drinking water were sought during a period of 10 years in the two cities of Newburgh and Kingston, New York. The water supply of Newburgh was fluoridated, one of the earliest in the country; Kingston with about 0.05 ppm in the community drinking water was maintained as a control city. Thorough examinations of hundreds of children annually showed beyond doubt that growth, as revealed by height, weight, bone age estimated from wrist and knee radiographs, and other indices, was exactly comparable in the Newburgh and in the Kingston children. A few more cortical defects were found in the radiographs of the bones of the Newburgh children; in the opinion of the radiologist, Dr. Caffey, the difference was within the limits of normal variation.

The question of adverse effects on reproduction has been examined. Large doses of fluoride interfere with fertility and normal reproductive performance. Pregnant animals of several species have been fed fluoride without teratogenic effects. Relatively large doses of fluorides to female rats during gestation caused changes in the jaw bone and in the teeth of neonatal rats.

Chronic Fluorosis: Crippling fluorosis was first described as an industrial disease. X-ray examination showed (a) that the broad ligaments had calcified; (b) that the skeleton exhibited generalized hypermineralization with "motheaten" areas of hypomineralization; and (c) that exostoses projected both from flat and from long bones. Crippling fluorosis developed when men inhaled as dust 20 to 80 or perhaps more mg F per day for protracted periods, perhaps 10 to 20 years. This readily preventable illness should never recur. When fluoride exposures are unavoidable, urine analyses offer a reliable quantitative index of the exposures. The lengthy latent period permits the degree of exposure to be identified and controlled by appropriate safety measures. Radiographic examination will reveal asymptomatic osteosclerosis long before joint function is impaired. Skeletal fluoride is mobilized and slowly removed from the body when exposure is reduced.

Preliminary studies of the osteosclerotic changes have by no means clarified the mechanism of this effect. Recent attempts to understand the mechanism have produced several remarkable findings.

(a) The rapidity of calcium 47 deposition in the skeleton of osteoporotic subjects was reduced after prolonged fluoride treatment, i.e., less bone participated in the rapid exchange. Remineralization, or new bone formation, which reduced the amount of bone "available" to the circulation would plausibly account for such a difference.

(b) A narrowing of the x-ray diffraction peaks of the bones of fluoride-treated men or animals is interpreted as an increase in the average crystal size of the apatite mineral. Larger crystals possess smaller surface to weight ratios and have, therefore, less exchangeable calcium. Furthermore, the dissolution rates of larger crystals are less than of smaller ones, an effect which together with the considerably lower solubility attributed to the fluorapatite lattice would contribute greater "stability" to bone.

(c) Paradoxically, prolonged treatment with large doses of fluoride reduces the incorporation of proline into bone collagen. Carbon 14-hydroxyproline tends to accumulate in the cell rather than in collagen. Such an interference with osteocytic metabolism would be expected to accompany a reduction in new bone formation. Perhaps this effect accounts for the fact that in patients suffering from crippling fluorosis certain local areas of bone may become

hypomineralized; in these areas, described as "moth-eaten," bone formation is notably impaired.

(d) Several observations direct attention to an intriguing possibility that the parathormone is somehow involved in the osteosclerotic response to repeated large doses of fluoride. The parathyroid gland enlarges and becomes hyperplastic in sheep and in rabbits receiving 200 ppm F in their rations. According to a complicated hypothesis, the parathyroid-mediated osteosclerosis involves two sequences. First, parathyroid stimulation. Fluoride deposited in bone renders the bone calcium somewhat less available, thereby lowering slightly the concentration of blood calcium which stimulates parathormone secretion, increasing the activity of the bone cells and reestablishing the normal blood calcium. Second, increased collagen formation. Recent preliminary evidence indicates that a secondary effect of parathyroid stimulation occurring later than the well-established mobilization of bone mineral may, under certain circumstances, be a speeded-up collagen formation. In an animal chronically exposed to excessive amounts of fluoride, new bone formation might follow.

The term "mottled enamel" or dental fluorosis embraces several degrees of severity. "Very mild mottling" and "mild mottling" (the first and second degrees) describe hypoplasias that are not esthetically damaging, i.e., are now brown-stained teeth. Brown stain, accompanies only the more severe hypoplasias: "moderate mottling"—brown stain under a smooth enamel surface (third degree) and "severe mottling" —brown stain in teeth with pitted or grooved surfaces (fourth degree).

Dean's classic epidemiological studies of the incidence and severity of mottling in the permanent teeth of 2 to 14 year old residents of American communities were the drinking waters contained from traces up to several ppm F, established the increase in mottling with increasing F concentration above 1 ppm F. The community index of mottling, Dean's device for summarizing data, takes the average based on the two most severely mottled teeth for each child; the community index increases in a linear fashion with the logarithm of F concentration above 1 ppm. Brown stain from fluoride is not observed in communities in temperate climates if the drinking water contains 2 ppm F or less. Thus, in water fluoridation the safety margin against brown stain while not large is established with an exceptional reliability.

Mottled enamel develops only while teeth are forming prior to eruption. Excessive fluoride impairs the function of the ameloblasts, the cells that form the enamel, and hypoplasias result. Hypoplasias of the enamel surface are by no means uniquely due to fluoride; these changes are nonspecific at least to the extent that several other causative agents are known, e.g., trauma, vitamin deficiency, febrile illness. Even in communities with only traces of F in the drinking water, about one child in five has detectable nonspecific hypoplasia. With sufficiently elevated water F concentrations, brown stains develop, but not uniformly in every child.

Dental Caries: Despite the evidence that slowly accumulated during a score of years, of caries resistance conferred by fluoride, experts in dental health were slow to accept Dean's convincing demonstration that the DMF (decayed, missing and filled teeth) rates decreased with increasing F concentrations in community water supplies in temperate areas of the United States. The DMF rates in the permanent teeth of 12 to 14 year old children ranged from 6 to 10 "bad" teeth per child with traces of F in the water, to 4 to 5 with 0.5 ppm F, to 2 to 3 with 1 to 4 ppm F in the water. At 1 ppm F, the hazard of brown stain is minimal; this concentration in a temperate climate, thus offers optimal tooth health with minimal hazard of injury. Extensive studies in the succeeding score of years have established the wisdom of this choice. No ill-effects are established in any individual regardless of age or state of health in communities using fluoridated drinking water supplies with recommended concentrations (ranging from 1 ppm F down depending on the annual mean temperature to 0.7 ppm F). The fluoridation of public water supplies is widely acclaimed as one of the most important public health developments of our time.

ABSORPTION AND EXCRETION OF MERCURY IN MAN XV. OCCUPATIONAL EXPOSURE AMONG DENTISTS

Morris M. Joselow, PhD, Leonard J. Goldwater, MD, Antonio Alvarez, BS, and Jeanne Herndon, New York, New York, Arch Environ Health 17(1)39–43, July 1968.

To evaluate the occupational hazard of the use of mercury by dentists, determinations were made of (1) the total mercury and vapor concentrations in a group of urban dental offices; and (2) the urinary excretion of mercury by the dentists. In a small but significant proportion (14%) of these offices, mercury concentrations were found in excess of the threshold limit value, implying a lack of care in handling mercury. The average total mercury concentration was more than twice the average vapor concentration, clearly inferring that mercury particulates cannot be ignored in assessing the dental work environment. Absorption of mercury was evidenced by higher than "normal" urinary mercury levels, which correlated well with both the total ambient air concentrations and estimated exposure times.

Questions regarding the toxicity of mercury in dental practice have been raised almost since the time of the introduction of mercury amalgams. Even though some concern was expressed early for the risks to dental personnel by continuous handling of mercury, for the most part, attention was focussed on the hazards to the patient by absorption of mercury from the amalgam filling.

It has now been shown fairly well that the absorption and excretion of mercury by patients after about a week following the insertion of an amalgam filling is negligible, and that the use of mercury in dental practice may be considered innocuous to the patient.

However, the occupational hazard presented to dental personnel by their daily work with, and perhaps extensive exposure to, mercury has by no means been so well established. In most practices, many opportunities for absorption of mercury will occur. The mechanical compaction, trituration, and expression of mercury will occur. The mechanical compaction, trituration, and expression of excess mercury from the amalgam mass may permit direct skin contact with mercury; and during grinding and polishing it is almost impossible to avoid the generation of mercury vapor and a fine amalgam powder which can be breathed by both dentist and patient. Furthermore, the mercury metal itself will volatilize from open containers or from droplets on the floor or working table, providing another source of air contamination.

Probably because of the ease of measurement, the early attempts at assessing the mercury hazard depended almost exclusively on the determination of the mercury vapor concentration in the air of dental offices. Here conflicting findings and judgments have been reported. Vesterberg found mercury vapor values as high as 0.25 mg/cu m in dental offices in Sweden, more than twice the current threshold limit value (TLV) of 0.1 mg/cu m of the American Conference of Governmental Industrial Hygienists. In 1949, however Grossman found considerably lower values and concluded that the amount of mercury vapor with which the average dentist comes into contact is not toxic. Similar measurements of air values in dental offices in Sweden led to similar though somewhat more qualified conclusions. Both Dalhamn and Drykholm concluded that there was no serious risk of chronic mercury poisoning for dental personnel, under normal conditions.

More recent studies have led to more cautious views of mercury as a potential occupational hazard to dentists. Meyer found levels of mercury in the air that could for short periods of time range from 0.10 to up to four times the TLV for mercury, with the higher values being noted for short periods of time. Two cases of mercury intoxication among dental personnel were reported in 1963. In a 1965 British study which was based largely on determinations of the mercury content of the hair and fingernails of dental personnel, Nixon came to the conclusion that "chronic mercury poisoning (in some cases undiagnosed perhaps) may be a hazard to either the dentist or his staff."

Not to be discounted, in this review of the problem, are the periodic warnings that have appeared in medical and dental literature over the course of many years, on the potential mercury hazard to dentists. Perhaps the most alarming of these in the article by McCord, who gloomily surmised that "over the land at all times some thousands of dentists are the victims of mercury poisoning in varying degrees of severity."

Quite apparently, some difference of opinion exists regarding this hazard. A further complication to the problem is the fact that all of the foregoing reports that were based on air measurements of mercury must be considered of limited value since the instrumentation used was capable of measuring only the vapor form of mercury. A fine particulate mercury amalgam powder that may remain suspended in the air of the offices and breathed in along with the vapor can also be produced in dental work, and may account for considerably more of the mercury contamination than the vapor alone. So far as could be determined, none of the investigators cited determined the amount of the suspended mercury particulate matter, although several were aware that such particulate contamination did exist and could be significant.

Because of this obvious weakness of many of the foregoing studies and the uncertain picture that emerges on consideration of all of them, a new exploratory survey was undertaken (1) to determine the mercury vapor concentrations as well as the total mercury (vapor and particulates) levels in the air of active dental offices; and (2) to obtain some indications of the absorption of mercury occasioned by these air concentrations by determining the urinary mercury excretion of the practicing dentists.

Results

Considering the TLV for mercury of 0.1 mg/ cu m, it was shown that almost all of the premises surveyed showed vapor values below this level. However, when total mercury concentrations (vapor and particulates) are examined, it was shown that a small but significant percentage (14%) of the operating room levels exceeded concentrations of 0.1 mg/ cu m.

Of special interest was the finding that the average concentration for total mercury, 0.045 mg/ cu m, for all the offices surveyed, was more than twice the vapor concentration (0.020 mg/cu m), thus clearly demonstrating the significant contribution that particulates—largely ignored by previous investigators—can make to the contamination of the air of dental offices. By difference, the average particulate concentrations, 0.025 mg/ cu m, was somewhat higher than the average vapor concentration, but there were many individual offices, particularly where active amalgam work was in progress at the time of sampling, that showed total mercury values more than ten times the concurrent vapor levels.

Vapor levels in the waiting rooms for the most part paralleled the vapor levels in the offices. No analyses for total mercury were made in the air in the waiting rooms.

Of perhaps greater occupational significance are the urinary mercury contents of the dentists, particularly when these values are compared to "normal" values, i.e., values for a population with no known exposure to mercury. Goldwater reported that 80% of such a population showed no urinary mercury, i.e., values less than 5μg/liter. In the dental group, on the other hand, about 90% of the population did show mercury in their urine, in amounts that ranged from 10μg to 155 μg/liter. The dentists as a group are absorbing mercury is clearly indicated by these data.

Analysis of the data for correlation between the urinary mercury content and the total mercury content in the air was made. The correlation coefficient found was considered to be highly significant, inferring a strong direct relationship between mercury exposure and excretion among the dentists as a group.

A similar but somewhat weaker correlation was found between the urinary mercury levels and the estimated number of hours per week engaged in mercury work.

Both of the foregoing relationships clearly point to the occupational source and nature of the mercury excretion shown by the dental group. This direct relationship between mercury exposure and excretion is of special toxicological significance since exposure among dentists is of a relatively pure type, i.e., metallic mercury, uncomplicated by the presence of other mercurials often found in other occupational exposures.

Comment

The findings of this study—though limited to a small urban group of dentists—paint neither a grim picture of the mercury hazard nor do they exonerate this metal as a potential occupational problem.

Of the premises surveyed, 14% showed mercury concentrations in excess of what is considered good hygienic practice. If this is conservatively extrapolated to the nation's 100,000 practicing dentists—a risky procedure, to be sure—then thousands of dentists are being needlessly overexposed to mercury. This does not necessarily mean that thousands of dentists are at the same time being poisoned, as inferred by Dr. McCord in the statement quoted above, since the relationship between exposure even at levels above the TLV and mercury intoxication is by no means well established.

What can be concluded, however, is that mercury in dental practice can not be casually treated or dis-

missed as a potential source of trouble. Its use demands good hygienic practice—often found to be violated in this survey. Many dentists for example, still knead the amalgam mass in the palm of their hands. In squeezing the mass to express excess mercury—also done by hand—mercury droplets sometimes fall to the floor where they are allowed to remain and vaporize. In some offices, crevices at corners and along the walls—in which mercury droplets could collect and vaporize, particularly behind radiators—were apparent. Office decor and location were often selected without regard for the clean-up problem in the event of a mercury spill—always a probability when handling mercury. One of the highest vapor levels recorded in this survey was seen in a carpeted reception room, located unwisely between the work room and the operating room. It could easily be guessed that these high levels were due to occasional spills in carrying material between the two rooms or even in tracking mercury across the reception room. Once lodged in carpeting, mercury is almost impossible to remove. The usual cleaning method, with a vacuum sweeper, may serve only to disperse and further spread the contamination.

EDITOR'S SECTION

RESULTS OF STUDIES PERFORMED *IN VITRO* AND *IN VIVO* ON GAMMA GLOBULIN PREPARATIONS DERIVED FROM PLACENTAL AND NON-PLACENTAL SOURCES

All lots of gamma globulin preparations derived from placental sources (manufactured by Lederle Laboratories and Pitman-Moore) are contaminated with A and B blood group substance, as shown by hemagglutination inhibition assays. Approximately 167 μg/ml of B substance and 20 μg/ml A substance are present in these preparations.

All lots of gamma globulin preparations derived from non-placental sources (manufactured by Hyland Laboratories) are free of blood group substance contaminants.

The administration of placental gamma globulin (in doses of five ml given deep intramuscularly) resulted in isoantibody rises in all recipients. All recipients showed marked elevation in isohemolysin titers. Group O recipients showed rises in isoagglutinins and "immune" (non-neutralizeable) agglutinins as well. These changes were marked with respect to anti-B isoantibodies but were seen in anti-A isoantibodies as well.

Placental gamma globulin preparations are contaminated with large amounts of B and lesser amounts of A blood group substance, and represent a source of immunization when given to the human recipient. They likely represent a source for the increased incidence of "dangerous" universal donors among immunized group O individuals.—Army Medical Research Laboratory, Fort Knox, Kentucky.

ARE YOU BLINDING YOUR PATIENT BY LOWERING HIS BLOOD PRESSURE?

We're talking about *Glaucoma.*

We are all aware of the hazards of lowering systemic blood pressure too rapidly, and thereby precipitating cerebral hypoxia, but do we recognize a similar risk in the patient with chronic simple glaucoma? The lowered perfusion pressure in the ophthalmic artery and retinal vessels disturbs the delicate balance of pressures within the glaucomatous eye, and rapid deterioration of vision can occur. What appears to be a happy result on the sphygmomanometer may have a devastating effect on the integrity and vitality of the optic nerve. Thus, we should be well aware of the intraocular pressure before lowering systemic blood pressure.

Two of every hundred people over 40 have a significantly increased intraocular pressure. We, the specialists who pride ourselves on the "complete examination," are, from all we can find out, not doing simple ocular tonometry as a routine procedure. Why not? No disrobing as in Pap smearing. No needles as in blood sugar testing. Just resting a tonometer on the cornea.

Presented in behalf of the Neurological and Sensory Disease Control Program of the National Center for Chronic Disease Control, Arlington, Va.

LIST OF NEW NAVAL HOSPITALS

I. Station Hospitals Redesignated as Naval Hospitals on 1 July 1968

	Operating Beds
Naval Hospital, Cherry Point, N. C.	55

Naval Hospital, Lemoore, Calif. 40
U.S. Naval Hospital, Naples, Italy 88
Naval Hospital, Patuxent River, Md. ... 50
Naval Hospital, Port Hueneme, Calif. .. 30
Naval Hospital, Quonset Point, R. I. 55
U.S. Naval Hospital, Rota, Spain 33
U.S. Naval Hospital, Taipei, Taiwan 40
Naval Hospital, Whidbey Island, Oak Harbor, Wash. 25

II. Proposed Station Hospitals Redesignated as Naval Hospitals

Naval Hospital, Albany, Ga. 30
U.S. Naval Hospital, Roosevelt Roads, P. R. 39

III. New Naval Hospital Commissioned on 1 July 1968

Naval Hospital, Orlando, Fla. 175

Definitive and Professional Criteria for Naval Hospitals or U.S. Naval Hospitals

A. *Definitive:*

1. Have at least 25 operating beds.
2. Serve a minimum population of 10,000.
3. Serve an active duty, military population of which at least 75% are not members of the command to which the facility belongs.

B. *Professional:*

1. Provide for the care of patients who stay in the hospital on the average of at least 24 hours per admission.
2. Have an organized medical staff (which may include doctors of osteopathy and dentists) providing medical services more intensive than those required merely for board, room, personal services, and general nursing care.
3. Provide minimal surgical facilities (including operating/delivery rooms) and relatively complete diagnostic and treatment facilities for all patients.
4. Provide diagnostic radiology services to support the medical services provided.
5. Provide clinical laboratory services in support of the medical services provided.
6. Provide pharmaceutical services as required.
7. Provide registered nurse supervision and such other nursing services as necessary to provide 24-hour patient care.
8. Provide adequate outpatient care.
9. Provide in-house training in accordance with instructions of the Surgeon General of the Navy.
10. Normally be staffed for and capable of self administration.

CHART OF GRADING EQUIVALENTS

Writing reports and grading the performance of individuals are most important but also difficult. Areas of difficulty are discrepancies between the numerical grade and the word description for which evaluation is requested and variation of reporting standards from institution to institution. This is true of all report forms but is especially evident on the Resident Ninth Month Report (MED 1520–3). It is obvious that the reporting format or understanding of the grades and comments should be as uniform as possible to ensure fairness to those being reported upon.

It is therefore suggested that the Military Numerical System, first column of the chart, be used by all Chiefs of Services in preparing the Resident Ninth Month Report. The other columns are provided only for comparison with other marking systems.

Military Numercial System	Letter System	Percentage System	Word System
3.6—4.0	A	90-100	Excellent
3.2—3.5	B	80-89	Good
2.8—3.1	C	70-79	Fair
2.4—2.7	D	60-69	Poor
2.0—2.3	F	—	Fail

AWARDS AND HONORS

Navy Cross

Crawford, Charles H., HM3 USN
Grant, Gollie L., HN USN

Silver Star

Schon, John E., HM2 USN

Legion of Merit

Grisamore, Jennings M., CDR MC USN
Kyes, Frank M., RADM DC USN
Murray, Dermot A., CAPT MC USN
Sierchio, Gerald P., CDR MC USN

Bronze Star

Havens, Joe B., HMCS USN

Air Medal

Althauser, Robert V., Jr., LT MSC USNR

Navy Commendation Medal

Alexander, Charles E., Jr., CDR MC USN
Austin, Gary L., HM3 USN

Burr, John B., CDR MC USN
Cannon, Mary F., CDR USNR
Carey, Larry C., LCDR MC USN
Dietz, Bruce J., LCDR MSC USN
Horner, Michael M., HM2 USN
Jenkins, Elmer E., LT MSC USNR
Lockman, William A., Jr., HM1 USNR (TAR)
Lubin, Alvin H., LT MC USNR
Mathis, Jimmy C., HN USN

Navy Achievement Medal

Aaron, Alvin "J", LCDR MSC USN
Henderson, Jack T., LT MSC USN
Johnson, Jay D., HMCM USN
Kvale, Paul A., LT USN
Marrujo, Martin, HM3 USN
Vorosmarti, James., Jr., LCDR MC USN

Joint Service Commendation Medal

Mason, Donald E., HMC USN

Letter of Commendation

Anderson, John P., Jr., LT MC USN
Kluth, William J., DTC USN
Lyman, Harold J., Jr., DTC USN
Trout, Aubrey A., HMC USN

Letter of Appreciation

Burke, V. R., DTCM USN
Stover, John H., Jr., CAPT MC USN

AVAILABILITY OF PSYCHIATRIC RESIDENCIES IN NAVAL HOSPITALS

The Neuropsychiatry Branch announces the availability of vacancies in the approved Navy psychiatric residency training program.

Each year there are only eleven openings for Navy psychiatric residents beginning at the first year level. The Navy hospitals which offer fully-approved, three-year residency training programs in psychiatry are Bethesda, Maryland; Oakland, California; and Philadelphia, Pennsylvania.

Prospective residents often ask whether a Naval hospital can offer completely satisfactory residency training utilizing its own facilities and at the same time meet the requirements of the various accrediting committees. The same question could be asked of any hospital, civilian or military. The Navy teaching staffs are highly qualified, specially selected individuals. The Navy's psychiatric residency training program, as necessary, affiliates with local civilian psychiatric facilities in rounding out certain aspects of the program. Affiliation with state psychiatric hospitals affords extensive experience with chronic, psychotic patients. Affiliations are also made in one or more of the three programs for the purpose of acquiring experience in child guidance clinics, outpatient clinics, and in neurology. Civilian consultants participate extensively in the program by conducting regular seminars and supervising long-term therapy cases. The training experience in Navy hospitals includes inpatient and outpatient psychiatry ranging through the entire diagnostic spectrum. Types of therapy taught and utilized include all that are available, i.e., chemotherapy, individual and group psychotherapy, somatic therapy, occupational and milieu therapies. Male and female patients of all ages are seen for evaluation and treatment as indicated. Each training hospital is located in a metropolitan area where there are available academic lectures, short courses, and medical schools with excellent psychiatric departments. The psychiatric training program is further enhanced by relevant research programs and clinical studies of considerable variety. Thus, it can be seen, the resident is exposed to and guided through an extensive range of clinical and academic psychiatry.

Upon completion of residency training, Navy psychiatrists have available a wide variety of assignments offering diverse opportunities and professional challenges, ranging from assignment to the staff of training hospitals to duty as a psychiatrist aboard a hospital ship or with a Marine Division. Each assignment includes ongoing professional experience as well as increasing responsibilities commensurate with the individual's training, experience, and motivation. Tours of duty are relatively stable, depending upon the individual situation and needs of the service. The career Navy psychiatrist can expect to progress to Board certification, again depending upon his own motivation, and to increasingly responsible assignments up to Chief of the Neuropsychiatry Service of a residency training hospital.

Guidelines for application by medical officers for this program are provided in BUMED Instruction 1520.10C of 26 January 1965 (which is currently in process of being revised to 1520.10D). Applications are reviewed by the Surgeon General's Advisory Board which recommends candidates as qualified and acceptable for residency training. Although most residencies start in July of each year, this is not a rigid schedule since vacancies occur at other times of the year varying with positions available at individual hospitals resulting from completion of residency training by other individuals.

Inquiry for further details can be made directly to: Neuropsychiatry Branch (Code 313)
Bureau of Medicine and Surgery
Navy Department
Washington, D.C. 20390

TRAINING PROGRAM IN PREVENTIVE MEDICINE

The Navy sponsors a formal residency training program in Preventive Medicine, meeting the requirements of the American Board of Preventive Medicine.

The program consists of one academic year of postgraduate work in a civilian institution leading to a Master of Public Health degree, followed by two years of approved Navy training which may be in-service or at selected civilian Health Departments. The entire program is under the guidance of a civilian academic institution and leads to certification in General Preventive Medicine.

Applications should be submitted in accordance with BUMED INSTRUCTION 1520.10D. Applications for the 1969 residency training program will be considered in late October or early November 1968 and should be received in the Bureau of Medicine and Surgery, Code 316, as soon as possible.

FAR EAST CHAPTER ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES 2ND ANNUAL MEETING

The second annual meeting of the Far East Chapter of the Association of Military Surgeons will be held from 31 October through 2 November 1968 at Yokosuka, Japan. The host for this year's meeting will be CAPT Arthur R. Errion, MC USN, Force Medical Officer, Commander U.S. Naval Forces, Japan.

The purpose of the meeting is to facilitate the tri-service and interarea exchange of medical techniques, methods and experiences. During the two day professional meeting, five separate sections will run concurrently; (1) Medical; (2) Dental; (3) Veterinary; (4) Nursing; (5) Administrative and Allied Medical Sciences. These will be interspersed by panels of experts discussing topics of current general interest. These meetings are open to all officer personnel working in the health sciences whether or not they are members of th Association.

Officers interested in presenting a paper should contact CDR E. Fisher Coil, MC USN, Chairman, Program Committee, Association of Military Surgeons, U.S. Naval Hospital, FPO Seattle 98765. For registration information, inquiries should be directed to LTJG P. L. Bash at the same address. All interested health services officers are invited to attend.

In Memoriam

RADM Bertram Groesbeck, Jr., MC USN (Ret)
CAPT Lynn S. Beals, MC USN (Ret)
CAPT Leslie K. MacClatchie, MC USN (Ret)
CAPT Robert S. Simpson, MC USN (Ret)
CAPT Fred B. Smith, MC USN (Ret)
CAPT John W. Troy, MC USN (Ret)
CAPT Delbert G. Willard, MC USNR (Ret)
CDR Nathaniel H. Matros, MC USN (Ret)
CDR Clarence N. Smith, MC USN (Ret)
CDR Tommie K. Watkins, MC USN
LCDR Robert B. Fitzgerald, MC USN
LCDR Kathleen M. Malloy, NC USN (Ret)
LT George Raymond Leake, MSC USN (Ret)
CHMEDSERWRNT (W–4) George W. Babcock, Jr., USN (Ret)
HN Donald E. Vanderschans, USN

DEPARTMENT OF THE NAVY

BUREAU OF MEDICINE AND SURGERY
WASHINGTON, D.C. 20390

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